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(54) Title: METHODS AND COMPOSITIONS FOR MODULATING SPHINGOSINE-1-PHOSPHATE (S1P) RECEPTOR ACTIVITY

(57) Abstract: The present invention relates to compounds which modulate the activity of the SI P1 receptor, the use of these compounds for treating conditions associated with signaling through the S1 P1 receptor, and pharmaceutical compositions comprising these compounds.

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Methods and Compositions for Modulating Sphingosine-1-Phosphate (S1P) Receptor Activity

Related Applications

This application claims the benefit of and priority to U.S. Provisional Patent Application Serial No. 60/601232, filed August13, 2004, and U.S. Provisional Patent Application Serial No. 60/646436, filed January 21, 2005, the entire contents of each of which are incorporated herein by reference.

Background of the invention

The sphingosine-1-phosphate (S1P) receptors 1-5 constitute a family of seven transmembrane G-protein coupled receptors. These receptors, referred to as S1P1 to S1P5, are activated via binding by sphingosine-1-phosphate, which is produced by the sphingosine kinase-catalyzed phosphorylation of sphingosine. S1P receptors are cell surface receptors involved in a variety of cellular processes, including cell proliferation and differentiation, cell survival, cell invasion, lymphocyte trafficking, and cell migration. Sphingosine-1-phosphate is found in plasma and a variety of other tissues, and exerts autocrine and paracrine effects, including regulating the secretion of growth factors.

Administration of S1P to an animal results in sequestration of lymphocytes into the lymph nodes and Peyers patches without causing lymphocyte depletion. This activity, which is of potential utility in treating diseases or conditions associated with inappropriate immune response, including transplant rejection and autoimmune diseases, is believed to proceed via activation of the S1P1 receptor. Administration of S1P in vivo also has negative effects, including hypotension and bradycardia, which are believed due to signaling through one or more of the other S1P receptors, S1P2 to S1P5. Accordingly, there is a great need in the art for compounds which are potent and selective agonists of the S1P1 receptor.

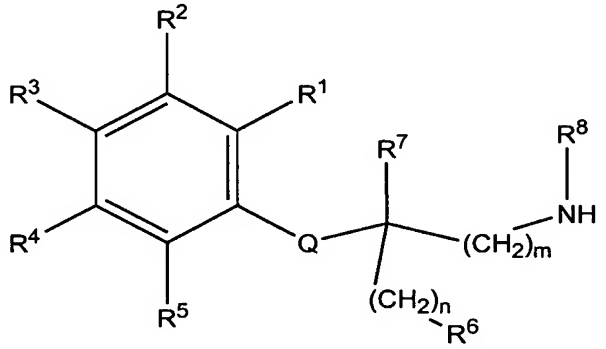
Summary of the Invention

The present invention relates to compounds which modulate the activity of the S1P1 receptor, the use of these compounds for treating conditions associated with signaling through the S1P1 receptor, and pharmaceutical compositions comprising these compounds.

The compounds of the present invention are characterized by a unique structure which imparts surprisingly improved properties to these compounds as compared to the

prior art compounds. Specifically, the compounds of the present invention are characterized by the presence of a substituted biphenyl moiety. This biphenyl moiety, in combination with an amide linkage within the core of the structure, enhances the selectivity of the compounds described herein for the S1P1 receptor versus other receptors, such as S1P3. The compounds of the present invention are further characterized by their potent binding to the S1P1 receptor.

In one embodiment, the invention pertains, at least in part, to compounds of Formula I:



(I),

wherein:

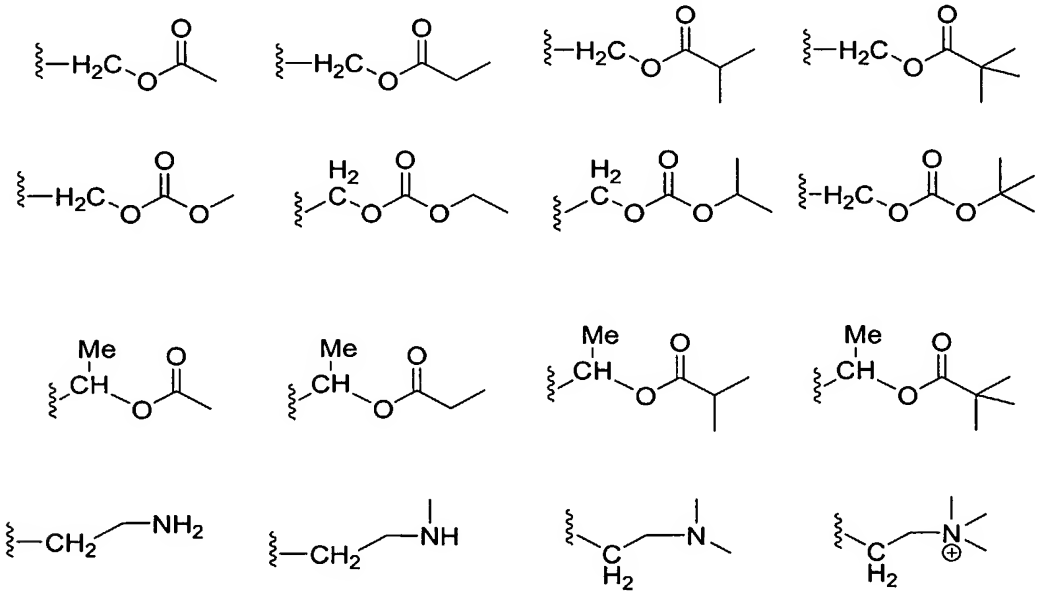
wherein one of R^3 and R^4 is C_4-C_{20}-alkyl, C_4-C_{20}-alkoxy; an oxaalkyl, thiaalkyl or azaalkyl group having a chain length of from 4 to 20 atoms, a phenyl or substituted phenyl group, a phenoxy or substituted phenoxy group, a substituted or unsubstituted arylalkyl group, a substituted or unsubstituted arylalkoxy group, a substituted or unsubstituted heteroarylalkyl group; or a substituted or unsubstituted heteroarylalkoxy group; and the other is hydrogen, halogen, cyano, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl (*e.g.*, trifluoromethyl), straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', where R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2;

R^1, R^2, and R^5 are each independently selected from the group consisting of hydrogen, halogen, cyano, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl (*eg.*,

trifluoromethyl), straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', where R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2;

Q is $-CH_2NR-$, $-CH_2NR(CO)-$, $-NH(CO)-$, $-(CO)NH-$, $-(CO)-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NRSO_2-$, $-SO_2-NR-$ or heteroaryl, where R is hydrogen or straight chain or branched C_1-C_6-alkyl;

R^6 is $-OH$, $-CO_2R^9$, $-CH_2=CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R^{10} and R^{11} are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



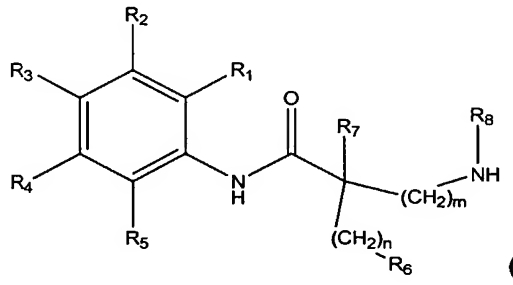
R^7 is H, C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, aryl, or together with R8 form a C_2-C_5-alkylene or a C_2-C_5-alkenylene group;

R^8 is H or C_1-C_6-alkyl; and

m and n are each, independently, an integer from 0 to 3;

provided that when R^4 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^3 and R^5 is not hydrogen; and when R^3 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^4 and R^5 is not hydrogen; and pharmaceutically acceptable salts thereof.

In another embodiment, the invention provides a compound of Formula II:



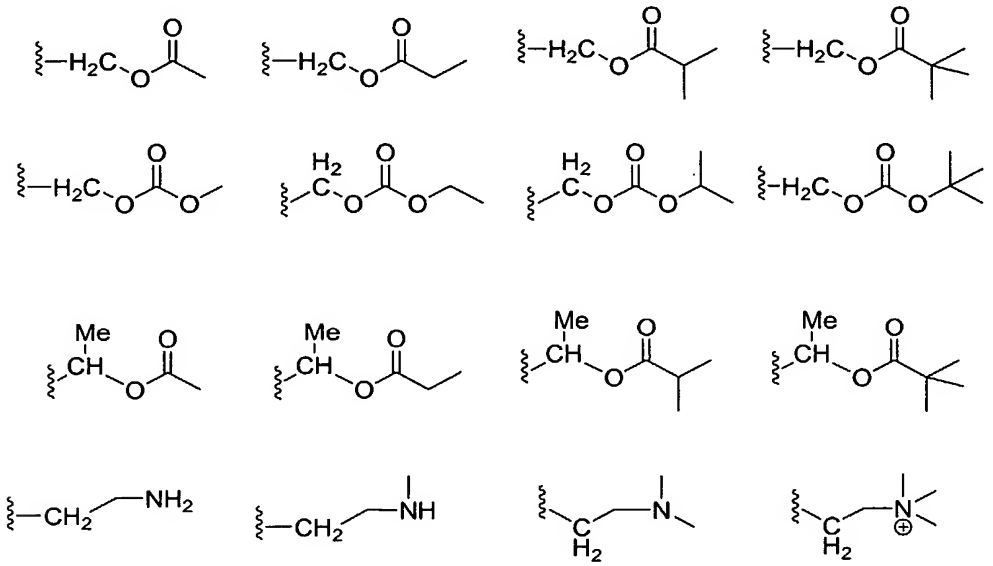
(II),

wherein one of R^3 and R^4 is C_4-C_{20}-alkyl, C_4-C_{20}-alkoxy; an oxaalkyl, thiaalkyl or azaalkyl group having a chain length of from 4 to 20 atoms, a phenyl or substituted phenyl group, a phenoxy or substituted phenoxy group, a substituted or unsubstituted arylalkyl group, a substituted or unsubstituted arylalkoxy group, a substituted or unsubstituted heteroarylalkyl group; or a substituted or unsubstituted heteroarylalkoxy group; and the other is hydrogen, halogen, cyano, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', where R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2;

R^1, R^2, and R^5 are each independently selected from the group consisting of hydrogen, halogen, cyano, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', where R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2;

Q is $-CH_2NR-$, $-CH_2NR(CO)-$, $-NH(CO)-$, $-(CO)NH-$, $-(CO)-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NRSO_2-$, $-SO_2-NR-$ or heteroaryl, where R is hydrogen or straight chain or branched C_1-C_6-alkyl;

R^6 is $-OH$, $-CO_2R^9$, $-CH_2=CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R^{10} and R^{11} are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



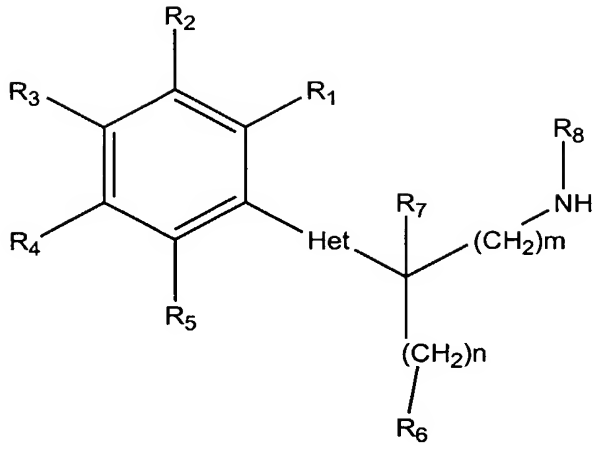
R^7 is H, C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, aryl, or together with R_8 form a C_2-C_5-alkylene or a C_2-C_5-alkenylene group;

R^8 is H or C_1-C_6-alkyl; and

m and n are each, independently, an integer from 0 to 3;

provided that when R^4 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^3 and R^5 is not hydrogen; and when R^3 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^4 and R^5 is not hydrogen; and pharmaceutically acceptable salts thereof.

In another embodiment, the invention provides compounds of Formula III:



(III),

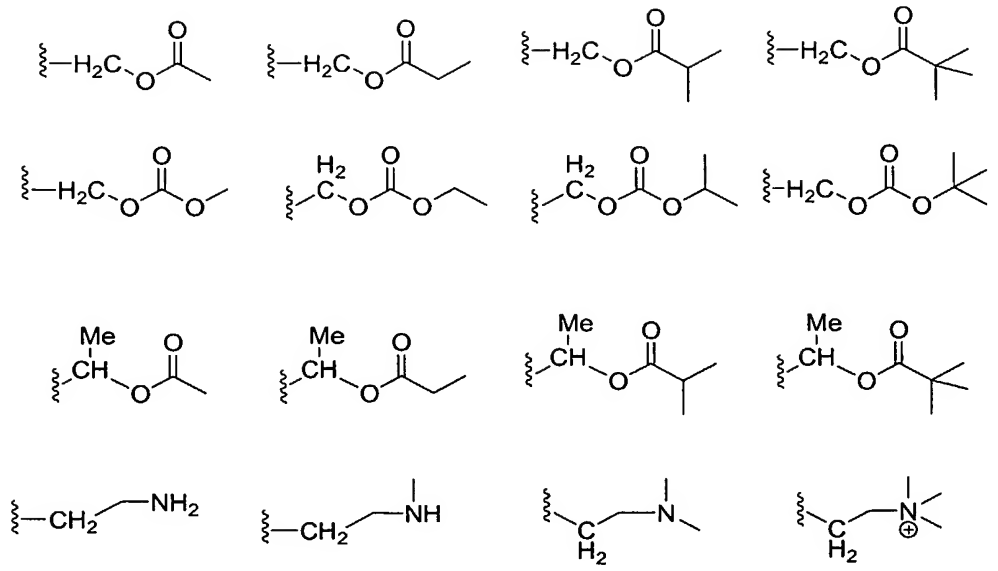
wherein:

Het is heteroaryl group;

R_3 and R_4 are each independently hydrogen, C_4-C_{20}-alkyl group, C_4-C_{20}-alkoxy group or an oxaalkyl, thiaalkyl or azaalkyl group having a chain length of from 4 to 20 atoms; a phenyl or substituted phenyl group; a phenoxy or substituted phenoxy group, a substituted or unsubstituted arylalkyl group, a substituted or unsubstituted arylalkoxy group, a substituted or unsubstituted heteroarylalkyl group; or a substituted or unsubstituted heteroarylalkoxy group;

R_1, R_2, and R_5 are each independently hydrogen, halogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', where R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2;

R^6 is –OH, $-CO_2R^9$, $-CH_2{=}CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R^{10} and R^{11} are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



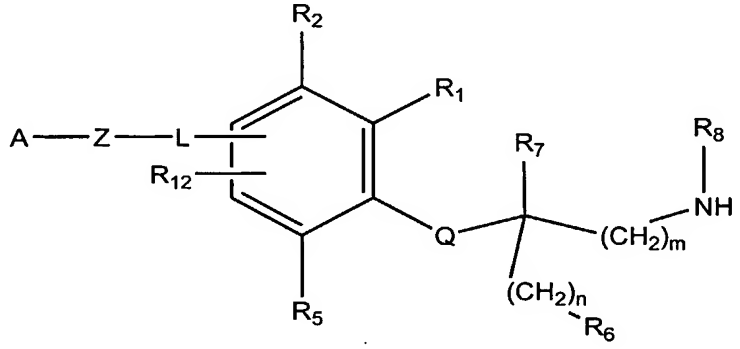
R_7 is H, C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, aryl or together with R_8 form a C_2-C_5-alkylene or a C_2-C_5-alkenylene group;

R_8 is H or C_1-C_6-alkyl;

m and n are each, independently, an integer from 0 to 3.

provided that when R^4 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^3 and R^5 is not hydrogen; and when R^3 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^4 and R^5 is not hydrogen; and pharmaceutically acceptable salts thereof.

In a preferred embodiment, the invention provides compounds of Formula IV:



(IV),

wherein:

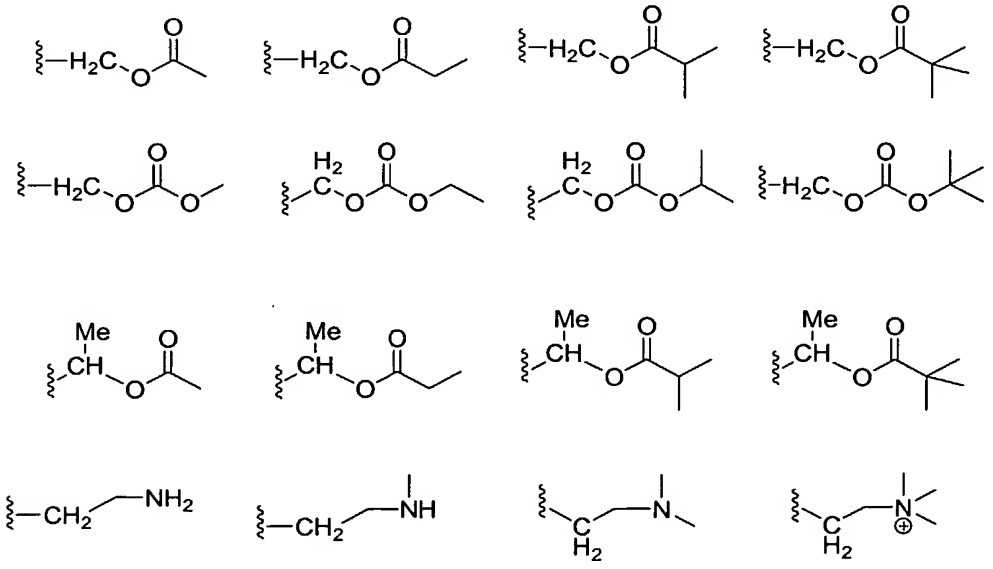
L is alkoxy, a covalent bond, substituted or unsubstituted alkyl, alkylcarbonyl, thioether, alkylsulfonyl, alkylcarbonylamino, alkylaminocarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, or substituted or unsubstituted heteroaryl;

Z and A are each independently substituted or unsubstituted aryl, wherein Z and A may be linked by a covalent bond, substituted or unsubstituted alkyl, NH, alkyloxy, O, thioether, S, aminocarbonyl, carbonylamino, carbonyloxy, or oxycarbonyl;

R^1, R^2, R^5 and R^{12} are each independently selected from the group consisting of hydrogen, halogen, cyano, substituted or unsubstituted aryl, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', wherein R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2;

Q is $-CH_2NR-$, $-CH_2NR(CO)-$, $-NH(CO)-$, $-(CO)NH-$, $-(CO)-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NRSO_2-$, $-SO_2-NR-$ or heteroaryl, where R is hydrogen or straight chain or branched C_1-C_6-alkyl;

R^6 is $-OH$, $-CO_2R^9$, $-CH_2=CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R10 and R11 are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



R^7 is H, C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, aryl, or together with R8 form a C_2-C_5-alkylene or a C_2-C_5-alkenylene group;

R^8 is H or C_1-C_6-alkyl; and

m and n are each, independently, an integer from 0 to 3;

provided that when R^4 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^3 and R^5 is not hydrogen; and when R^3 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^4 and R^5 is not hydrogen; and pharmaceutically acceptable salts thereof.

In yet another embodiment, the invention includes a method for treating a sphingosine 1-phosphate associated disorder in a subject. The method includes administering to the subject an effective amount of a compound of the invention, *e.g.*, a compound of Formula I or otherwise described herein, such that the subject is treated for the sphingosine 1-phosphate associated disorder.

In a further embodiment, the invention pertains, at least in part, to a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention, *e.g.*, a compound of Formula I or otherwise described herein, and a pharmaceutically acceptable carrier.

Brief Description of the Drawing

Figure 1 is a graph showing the results of the lymphopenia assay for certain compounds of the invention.

Detailed Description of the Invention

The compounds provided by the present invention are modulators of the S1P1 receptor and are preferably agonists of the S1P1 receptor. More preferably, the compounds are selective agonists of the S1P1 receptor. In addition to the S1P1 modulator compounds, the invention also provides pharmaceutical compositions comprising these compounds and methods of using these compounds for treating a condition associated an inappropriate immune response, such as transplant rejection or an autoimmune disease.

Definitions

As used herein, "alkyl" groups include saturated hydrocarbons having one or more carbon atoms, including straight-chain alkyl groups (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.), cyclic alkyl groups (or "cycloalkyl" or "alicyclic" or "carbocyclic" groups) (*e.g.*, cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.), branched-chain alkyl groups (isopropyl,

tert-butyl, *sec*-butyl, isobutyl, etc.), and alkyl-substituted alkyl groups (*e.g.*, alkyl-substituted cycloalkyl groups and cycloalkyl-substituted alkyl groups). The term "aliphatic group" includes organic moieties characterized by straight or branched-chains, typically having between 1 and 22 carbon atoms. In complex structures, the chains may be branched, bridged, or cross-linked. Aliphatic groups include alkyl groups, alkenyl groups, and alkynyl groups.

In certain embodiments, a straight-chain or branched-chain alkyl group may have 30 or fewer carbon atoms in its backbone, *e.g.*, C_1-C_{30} for straight-chain or C_3-C_{30} for branched-chain. In certain embodiments, a straight-chain or branched-chain alkyl group may have 20 or fewer carbon atoms in its backbone, *e.g.*, C_1-C_{20} for straight-chain or C_3-C_{20} for branched-chain, and more preferably 18 or fewer. Likewise, preferred cycloalkyl groups have from 4-10 carbon atoms in their ring structure, and more preferably have 4-7 carbon atoms in the ring structure. The term "lower alkyl" refers to alkyl groups having from 1 to 6 carbons in the chain, and to cycloalkyl groups having from 3 to 6 carbons in the ring structure.

Unless the number of carbons is otherwise specified, "lower" as in "lower aliphatic," "lower alkyl," "lower alkenyl," etc. as used herein means that the moiety has at least one and less than about 8 carbon atoms. In certain embodiments, a straight-chain or branched-chain lower alkyl group has 6 or fewer carbon atoms in its backbone (*e.g.*, C_1-C_6 for straight-chain, C_3-C_6 for branched-chain), and more preferably 4 or fewer. Likewise, preferred cycloalkyl groups have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term "C_1-C_6" as in "C_1-C_6 alkyl" means alkyl groups containing 1 to 6 carbon atoms.

Moreover, unless otherwise specified the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls," the latter of which refers to alkyl groups having substituents replacing one or more hydrogens on one or more carbons of the hydrocarbon backbone. Such substituents may include, for example, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclic, alkylaryl, or aromatic (including heteroaromatic) groups.

An "arylalkyl" group is an alkyl group substituted with an aryl group (*e.g.*, phenylmethyl (*i.e.*, benzyl)). An "alkylaryl" moiety is an aryl group substituted with an alkyl group (*e.g.*, *p*-methylphenyl (*i.e.*, *p*-tolyl)). The term "*n*-alkyl" means a straight-chain (*i.e.*, unbranched) unsubstituted alkyl group. An "alkylene" group is a divalent analog of the corresponding alkyl group. Examples of alkylene groups include ethylene ($-CH_2CH_2-$), propylene ($-CH_2CH_2CH_2-$), butylene ($-CH_2CH_2CH_2CH_2-$) and 1-methyethylene ($-CH(CH_3)CH_2-$). The terms "alkenyl", "alkynyl" and "alkenylene" refer to unsaturated aliphatic groups analogous to alkyls, but which contain at least one double or triple carbon-carbon bond respectively. Examples of alkenylene groups include ethenylene (-CH=CH-), propenylene ($-CH=CHCH_2-$), 2-butenylene ($-CH_2CH=CHCH_2-$) and 1-methyethenylene ($-C(CH_3)CH-$). Suitable alkenyl and alkynyl groups include groups having 2 to about 12 carbon atoms, preferably from 2 to about 6 carbon atoms.

The term "aromatic group" or "aryl group" includes unsaturated and aromatic cyclic hydrocarbons (*e.g.*, benzyl or phenyl) as well as unsaturated and aromatic heterocycles containing one or more rings. Aryl groups may also be fused or bridged with a bond (*e.g.*, biphenyl), alicyclic or heterocyclic rings that are not aromatic so as to form a polycycle (*e.g.*, tetralin). An "arylene" group is a divalent analog of an aryl group.

The term "heterocyclic group" includes closed ring structures analogous to carbocyclic groups in which one or more of the carbon atoms in the ring is an element other than carbon, for example, nitrogen, sulfur, or oxygen. Heterocyclic groups may be saturated or unsaturated. Additionally, heterocyclic groups (such as pyrrolyl, pyridyl, isoquinolyl, quinolyl, purinyl, and furyl) may have aromatic character, in which case they may be referred to as "heteroaryl" or "heteroaromatic" groups.

Unless otherwise stipulated, aryl and heterocyclic (including heteroaryl) groups may also be substituted at one or more constituent atoms. Examples of heteroaromatic and heteroalicyclic groups may have 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O, or S heteroatoms. In general, the term "heteroatom" includes atoms of any element other than carbon or hydrogen, preferred examples of which include nitrogen, oxygen, sulfur, and phosphorus. Heterocyclic groups may be saturated or unsaturated or aromatic.

Examples of heterocycles include, but are not limited to, acridinyl; azocinyl; benzimidazolyl; benzofuranyl; benzothiofuranyl; benzothiophenyl; benzoxazolyl; benzthiazolyl; benztriazolyl; benztetrazolyl; benzisoxazolyl; benzisothiazolyl; benzimidazolinyl; carbazolyl; 4aH-carbazolyl; carbolinyl; chromanyl; chromenyl; cinnolinyl; decahydroquinolinyl; 2H,6H-1,5,2-dithiazinyl;

dihydrofuro[2,3-b]tetrahydrofuran; furanyl; furazanyl; imidazolidinyl; imidazolinyl; imidazolyl; 1H-indazolyl; indolenyl; indolinyl; indolizinyl; indolyl; 3H-indolyl; isobenzofuranyl; isochromanyl; isoindazolyl; isoindolinyl; isoindolyl; isoquinolinyl; isothiazolyl; isoxazolyl; methylenedioxyphenyl; morpholinyl; naphthyridinyl; octahydroisoquinolinyl; oxadiazolyl; 1,2,3-oxadiazolyl; 1,2,4-oxadiazolyl; 1,2,5-oxadiazolyl; 1,3,4-oxadiazolyl; oxazolidinyl; oxazolyl; oxazolidinyl; pyrimidinyl; phenanthridinyl; phenanthrolinyl; phenazinyl; phenothiazinyl; phenoxathiinyl; phenoxazinyl; phthalazinyl; piperazinyl; piperidinyl; piperidonyl; 4-piperidonyl; piperonyl; pteridinyl; purinyl; pyranyl; pyrazinyl; pyrazolidinyl; pyrazolinyl; pyrazolyl; pyridazinyl; pyridooxazole; pyridoimidazole; pyridothiazole; pyridinyl; pyridyl; pyrimidinyl; pyrrolidinyl; pyrrolinyl; 2H-pyrrolyl; pyrrolyl; quinazolinyl; quinolinyl; 4H-quinolizinyl; quinoxalinyl; quinuclidinyl; tetrahydrofuranyl; tetrahydroisoquinolinyl; tetrahydroquinolinyl; tetrazolyl; 6H-1,2,5-thiadiazinyl; 1,2,3-thiadiazolyl; 1,2,4-thiadiazolyl; 1,2,5-thiadiazolyl; 1,3,4-thiadiazolyl; thianthrenyl; thiazolyl; thienyl; thienothiazolyl; thienooxazolyl; thienoimidazolyl; thiophenyl; triazinyl; 1,2,3-triazolyl; 1,2,4-triazolyl; 1,2,5-triazolyl; 1,3,4-triazolyl; and xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl; furanyl; thienyl; pyrrolyl; pyrazolyl; pyrrolidinyl; imidazolyl; indolyl; benzimidazolyl; 1H-indazolyl; oxazolidinyl; benzotriazolyl; benzisoxazolyl; oxindolyl; benzoxazolinyl; and isatinoyl groups. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

A common hydrocarbon aryl group is a phenyl group having one ring. Two-ring hydrocarbon aryl groups include naphthyl, indenyl, benzocyclooctenyl, benzocycloheptenyl, pentalenyl, and azulenyl groups, as well as the partially hydrogenated analogs thereof such as indanyl and tetrahydronaphthyl. Exemplary three-ring hydrocarbon aryl groups include acephthylenyl, fluorenyl, phenalenyl, phenanthrenyl, and anthracenyl groups.

Aryl groups also include heteromonocyclic aryl groups, *i.e.*, single-ring heteroaryl groups, such as thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, and pyridazinyl groups; and oxidized analogs thereof such as pyridonyl, oxazolonyl, pyrazolonyl, isoxazolonyl, and thiazolonyl groups. The corresponding hydrogenated (*i.e.*, non-aromatic) heteromonocylic groups include pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl and piperidino, piperazinyl, and morpholino and morpholinyl groups.

Aryl groups also include fused two-ring heteroaryls such as indolyl, isoindolyl, indolizinyl, indazolyl, quinolinyl, isoquinolinyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, chromenyl, isochromenyl, benzothienyl, benzimidazolyl,

benzothiazolyl, purinyl, quinolizinyl, isoquinolonyl, quinolonyl, naphthyridinyl, and pteridinyl groups, as well as the partially hydrogenated analogs such as chromanyl, isochromanyl, indolinyl, isoindolinyl, and tetrahydroindolyl groups. Aryl groups also include fused three-ring groups such as phenoxathiinyl, carbazolyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxazinyl, and dibenzofuranyl groups.

Some typical aryl groups include substituted or unsubstituted 5– and 6–membered single–ring groups. In another aspect, each Ar group may be selected from the group consisting of substituted or unsubstituted phenyl, pyrrolyl, furyl, thienyl, thiazolyl, isothiaozolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isooxazolyl, pyridinyl, pyrazinyl, pyridazinyl, and pyrimidinyl groups. Further examples include substituted or unsubstituted phenyl, 1-naphthyl, 2-naphthyl, biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl groups.

The term "amine" or "amino," as used herein, refers to an unsubstituted or substituted moiety of the formula $-NR^aR^b$, in which R^a and R^b are each independently hydrogen, alkyl, aryl, or heterocyclyl, or R^a and R^b, taken together with the nitrogen atom to which they are attached, form a cyclic moiety having from 3 to 8 atoms in the ring. Thus, the term amino includes cyclic amino moieties such as piperidinyl or pyrrolidinyl groups, unless otherwise stated. Thus, the term "alkylamino" as used herein means an alkyl group having an amino group attached thereto. Suitable alkylamino groups include groups having 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms. The term amino includes compounds or moieties in which a nitrogen atom is covalently bonded to at least one carbon or heteroatom. The term "dialkylamino" includes groups wherein the nitrogen atom is bound to at least two alkyl groups. The term "arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. The term "alkylarylamino" refers to an amino group which is bound to at least one alkyl group and at least one aryl group. The term "alkaminoalkyl" refers to an alkyl, alkenyl, or alkynyl group substituted with an alkylamino group. The term "amide" or "aminocarbonyl" includes compounds or moieties which contain a nitrogen atom which is bound to the carbon of a carbonyl or a thiocarbonyl group. The term "azaalkyl" refers to an alkyl group in which one or more $-CH_2-$ units have been replaced by an -N(R)- group, where R is hydrogen or C_1-C_4-alkyl.

If an azaalkyl group includes two or more N(R) groups, any two N(R) groups are separated by one or more carbon atoms.

The terms "alkylthio" or "thiaalkoxy" refers to an alkyl group, having a sulfhydryl group attached thereto. Suitable alkylthio groups include groups having 1 to about 12 carbon atoms, preferably from 1 to about 6 carbon atoms. The term "thiaalkyl" refers to an alkyl group in which one or more $-CH_2-$ units have been replaced by a sulfur atom. If a thiaalkyl group includes two or more sulfur atoms, any two sulfur atoms are separated by one or more carbon atoms.

The term "alkylcarboxyl" as used herein means an alkyl group having a carboxyl group attached thereto.

The term "alkoxy" as used herein means an alkyl group having an oxygen atom attached thereto. Representative alkoxy groups include groups having 1 to about 12 carbon atoms, preferably 1 to about 6 carbon atoms, *e.g.,* methoxy, ethoxy, propoxy, *tert*-butoxy and the like. Examples of alkoxy groups include methoxy, ethoxy, isopropyloxy, propoxy, butoxy, and pentoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, *etc.*, as well as perhalogenated alkyloxy groups. The term "oxaalkyl" refers to an alkyl group in which one or more $-CH_2-$ units have been replaced by an oxygen atom. If an oxaalkyl group includes two or more oxygen atoms, any two oxygen atoms are separated by one or more carbon atoms.

The term "acylamino" includes moieties wherein an amino moiety is bonded to an acyl group. For example, the acylamino group includes alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

The terms "alkoxyalkyl", "alkylaminoalkyl" and "thioalkoxyalkyl" include alkyl groups, as described above, which further include oxygen, nitrogen or sulfur atoms replacing one or more carbons of the hydrocarbon backbone.

The term "carbonyl" or "carboxy" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom. Examples of moieties which contain a carbonyl include aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc.

The term "ether" or "ethereal" includes compounds or moieties which contain an oxygen atom bonded to two carbon atoms. For example, an ether or ethereal group includes "alkoxyalkyl" which refers to an alkyl, alkenyl, or alkynyl group substituted with an alkoxy group.

The term "nitro" means $-NO_2$; the term "halogen" or "halogen" or "halo" designates -F, -Cl, -Br or -I; the term "thiol," "thio," or "mercapto" means SH; and the term "hydroxyl" or "hydroxy" means -OH.

The term "acyl" refers to a carbonyl group that is attached through its carbon atom to a hydrogen (*i.e.*, a formyl), an aliphatic group (*e.g.*, acetyl), an aromatic group (*e.g.*, benzoyl), and the like. The term "substituted acyl" includes acyl groups where one or more of the hydrogen atoms on one or more carbon atoms are replaced by, for example, an alkyl group, alkynyl group, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

Unless otherwise specified, the chemical moieties of the compounds of the invention, including those groups discussed above, may be "substituted or unsubstituted." In some embodiments, the term "substituted" means that the moiety has substituents placed on the moiety other than hydrogen (*i.e.*, in most cases, replacing a hydrogen), which allow the molecule to perform its intended function. Examples of substituents include moieties selected from straight or branched alkyl (preferably C_1-C_5), cycloalkyl (preferably C_3-C_8), alkoxy (preferably C_1-C_6), thioalkyl (preferably C_1-C_6), alkenyl (preferably C_2-C_6), alkynyl (preferably C_2-C_6), heterocyclic, carbocyclic, aryl (*e.g.*, phenyl), aryloxy (*e.g.*, phenoxy), arylkyl (*e.g.*, benzyl), aryloxyalkyl (*e.g.*, phenyloxyalkyl), arylacetamidoyl, alkylaryl, heteroaralkyl, alkylcarbonyl and arylcarbonyl or other such acyl group, heteroarylcarbonyl, and heteroaryl groups, as well as $(CR'R'')_{0-3}NR'R''$ (*e.g.*, $-NH_2$), $(CR'R'')_{0-3}CN$ (*e.g.*, -CN), $-NO_2$, halogen (*e.g.*, -F, -Cl, -Br, or -I), $(CR'R'')_{0-3}C(halogen)_3$ (*e.g.*, $-CF_3$), $(CR'R'')_{0-3}CH(halogen)_2$,

$(CR'R'')_{0-3}CH_2$(halogen), $(CR'R'')_{0-3}CONR'R''$, $(CR'R'')_{0-3}(CNH)NR'R''$, $(CR'R'')_{0-3}S(O)_{1-2}NR'R''$, $(CR'R'')_{0-3}CHO$, $(CR'R'')_{0-3}O(CR'R'')_{0-3}H$, $(CR'R'')_{0-3}S(O)_{0-3}R'$ (*e.g.*, $-SO_3H$), $(CR'R'')_{0-3}O(CR'R'')_{0-3}H$ (*e.g.*, $-CH_2OCH_3$ and $-OCH_3$), $(CR'R'')_{0-3}S(CR'R'')_{0-3}H$ (*e.g.*, -SH and $-SCH_3$), $(CR'R'')_{0-3}OH$ (*e.g.*, -OH), $(CR'R'')_{0-3}COR'$, $(CR'R'')_{0-3}$(substituted or unsubstituted phenyl), $(CR'R'')_{0-3}(C_3-C_8$ cycloalkyl), $(CR'R'')_{0-3}CO_2R'$ (*e.g.*, $-CO_2H$), and $(CR'R'')_{0-3}OR'$ groups, wherein R' and R" are each independently hydrogen, a C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, or aryl group; or the side chain of any naturally occurring amino acid.

In another embodiment, a substituent may be selected from straight or branched alkyl (preferably C_1-C_5), cycloalkyl (preferably C_3-C_8), alkoxy (preferably C_1-C_6), thioalkyl (preferably C_1-C_6), alkenyl (preferably C_2-C_6), alkynyl (preferably C_2-C_6), heterocyclic, carbocyclic, aryl (*e.g.*, phenyl), aryloxy (*e.g.*, phenoxy), aralkyl (*e.g.*, benzyl), aryloxyalkyl (*e.g.*, phenyloxyalkyl), arylacetamidoyl, alkylaryl, heteroaralkyl, alkylcarbonyl and arylcarbonyl or other such acyl group, heteroarylcarbonyl, or heteroaryl group, $(CR'R'')_{0-10}NR'R''$ (*e.g.*, $-NH_2$), $(CR'R'')_{0-10}CN$ (*e.g.*, -CN), NO_2, halogen (*e.g.*, F, Cl, Br, or I), $(CR'R'')_{0-10}C$(halogen)$_3$ (*e.g.*, $-CF_3$), $(CR'R'')_{0-10}CH$(halogen)$_2$, $(CR'R'')_{0-10}CH_2$(halogen), $(CR'R'')_{0-10}CONR'R''$, $(CR'R'')_{0-10}(CNH)NR'R''$, $(CR'R'')_{0-10}S(O)_{1-2}NR'R''$, $(CR'R'')_{0-10}CHO$, $(CR'R'')_{0-10}O(CR'R'')_{0-10}H$, $(CR'R'')_{0-10}S(O)_{0-3}R'$ (*e.g.*, $-SO_3H$), $(CR'R'')_{0-10}O(CR'R'')_{0-10}H$ (*e.g.*, $-CH_2OCH_3$ and $-OCH_3$), $(CR'R'')_{0-10}S(CR'R'')_{0-3}H$ (*e.g.*, -SH and $-SCH_3$), $(CR'R'')_{0-10}OH$ (*e.g.*, -OH), $(CR'R'')_{0-10}COR'$, $(CR'R'')_{0-10}$(substituted or unsubstituted phenyl), $(CR'R'')_{0-10}(C_3-C_8$ cycloalkyl), $(CR'R'')_{0-10}CO_2R'$ (*e.g.*, $-CO_2H$), or $(CR'R'')_{0-10}OR'$ group, or the side chain of any naturally occurring amino acid; wherein R' and R" are each independently hydrogen, a C_1-C_5 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, or aryl group, or R' and R" taken together are a benzylidene group or a $-(CH_2)_2O(CH_2)_2-$ group.

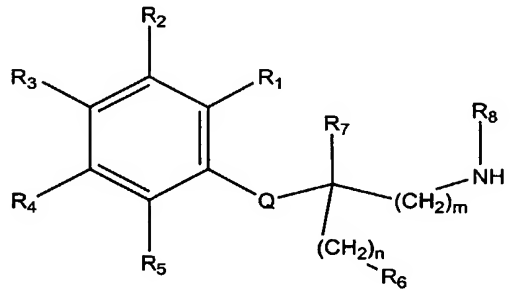
It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with the permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is meant to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. The permissible substituents can be one or more.

In some embodiments, a "substituent" may be selected from the group consisting of, for example, halogen, trifluoromethyl, nitro, cyano, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6

alkynyl, C_1-C_6 alkylcarbonyloxy, arylcarbonyloxy, C_1-C_6 alkoxycarbonyloxy, aryloxycarbonyloxy, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, arylthio, heterocyclyl, aralkyl, and aryl (including heteroaryl) groups.

Compounds of the Invention

In one embodiment, the invention pertains, at least in part, to compounds of Formula (I):



(I),

wherein:

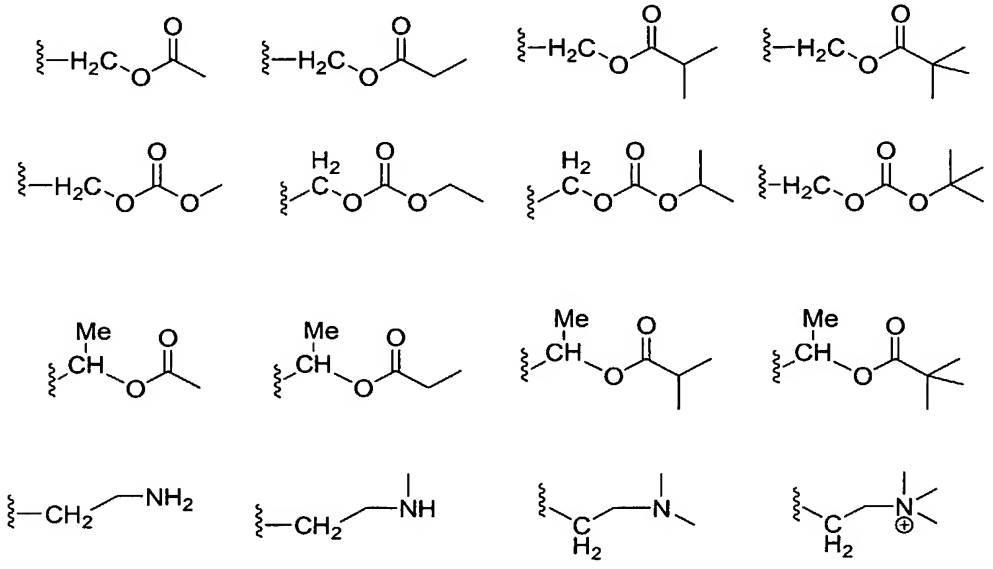
one of R_3 and R_4 is C_4-C_{20}-alkyl, C_4-C_{20}-alkoxy; an oxaalkyl, thiaalkyl or azaalkyl group having a chain length of from 4 to 20 atoms, a phenyl or substituted phenyl group, a phenoxy or substituted phenoxy group, a substituted or unsubstituted arylalkyl group, a substituted or unsubstituted arylalkoxy group, a substituted or unsubstituted heteroarylalkyl group; or a substituted or unsubstituted heteroarylalkoxy group; and the other is hydrogen, halogen, cyano, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', where R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2;

R^1, R^2, and R^5 are each independently selected from the group consisting of hydrogen, halogen, cyano, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', where R and R' are each independently

hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2;

Q is $-CH_2NR-$, $-CH_2NR(CO)-$, $-NH(CO)-$, $-(CO)NH-$, $-(CO)-$ $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NRSO_2-$, $-SO_2-NR-$ or heteroaryl, where R is hydrogen or straight chain or branched C_1-C_6-alkyl;

R^6 is $-OH$, $-CO_2R^9$, $-CH_2=CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R^{10} and R^{11} are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



R^7 is H, C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, aryl, or together with R8 form a C_2-C_5-alkylene or a C_2-C_5-alkenylene group;

R^8 is H or C_1-C_6-alkyl; and

m and n are each, independently, an integer from 0 to 3;

provided that when R^4 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^3 and R^5 is not hydrogen; and when R^3 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^4 and R^5 is not hydrogen; and pharmaceutically acceptable salts thereof;

provided that when Q is NH(C=O), O, or heteroaryl; R^6 is OH; n is 1-4; one of R^1, R^2, R^3, R^4, and R^5 is C_1-C_{18} alkyl, C_2-C_{18} alkenyl, C_2-C_{18} alkynyl, C_5-C_{18}-alkoxy, $(CH_2)_{1-10}O(CH_2)_{1-10}$, C_5-C_{10}(aryl), C_5-C_{10}(aryl)(C_1-C_{10}alkyl), C_5-C_{10}(heteroaryl), C_5-C_{10}(heteroaryl)(C_1-C_{10}alkyl), C_5-C_{10} cycloalkyl, C_5-C_{10}(cycloalkyl)-(C_1-C_5 alkyl), C_5-C_{10}alkoxy(aryl), C_5-C_{10}alkoxy(aryl)(C_1-C_{10} alkyl), C_5-C_{10}alkoxy(heteroaryl), C_5-C_{10}alkoxy(heteroaryl)(C_1-C_{10} alkyl), C_5-C_{10}alkoxy(cycloalkyl), or C_5-C_{10}alkoxy(cycloalkyl)(C_1-C_{10} alkyl); and one of R^1, R^2, R^3, R^4, and R^5 is H, halogen, NH_2, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylamino, C_1-C_6 alkylcyano, or C_1-C_6 alkylthio, then R^8 is not hydrogen;

provided that when Q is heteroaryl; one of R^1, R^2, R^3, R^4, and R^5 is alkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, alkyl (optionally substituted aryl), arylalkyl, or arylalkyl (optionally substituted (aryl); R^8 is hydrogen; n is 1; then R^6 is not OH;

and provided that when Q is NH(C=O); R^6 is OH; R^1, R^2, R^3, R^4, and R^5 are each independently halogen, hydrogen, amino, or alkyl; then R^8 is not hydrogen.

In a further embodiment, R^1 is hydrogen. In another further embodiment, R^2 is hydrogen, alkyl, or halogen (*e.g.*, fluoro, bromo, chloro or iodo).

In another further embodiment, R^3 is substituted or unsubstituted alkyl or cycloalkyl group. The alkyl R^3 group may be substituted with any substituent which allows the compound of Formula I to perform its intended function, *e.g.*, modulate sphingosine 1-phosphate receptor. Examples of such substituents include halogens and hydroxyl groups. Other examples of possible substituents for alkyl R^3 groups include substituted or unsubstituted arylthioether, alkylthioether, alkylsulfoxide, arylsulfoxide, arylsulfonyl and alkylsulfonyl groups.

In a further embodiment, R^3 is a substituted or unsubstituted alkoxy or cycloalkoxy group (*e.g.*, a C_1-C_{20} alkoxy group). In a further embodiment, the substituted R^3 alkoxy group is substituted with one or more substituted or unsubstituted aryl groups. These aryl groups may further be substituted with any substituent which allows the compounds of the invention to perform their intended function, *e.g.*, modulate sphingosine 1-phosphate 1 receptors. Examples of such substituents include alkoxy groups, such as methoxy, ethoxy, and propoxy. These alkoxy groups may further be substituted with any substituents such as halogens, hydroxyl groups, cyano groups, and other substituents described herein.

In another embodiment, R^3 is a substituted or unsubstituted aryloxy group, *e.g.*, a substituted or unsubstituted phenoxy group. Furthermore, the phenoxy group may further be substituted with one or more substituents which allow the compound of the invention to perform its intended function. Examples of such substituents include substituted or unsubstituted alkyl or substituted or unsubstituted aryl groups. Examples of aryl groups which may be used to substitute the phenoxy R^3 groups include substituted or unsubstituted phenyl groups. Examples of substituents for these phenyl groups include halogens, cyano, alkoxy, alkyl groups, or any of the other possible substituents described herein.

In another embodiment, R^3 is a substituted or unsubstituted aryl or heteroaryl group. The substituted aryl or heteroaryl R^3 group may further be substituted with one or more halogens, such as fluorine, chlorine, bromine, or iodine. It also may be substituted with any of the other substituents described herein.

In yet another embodiment, R^3 is a substituted or unsubstituted alkyl amino carbonyl or a substituted or unsubstituted aryl amino carbonyl. In yet another embodiment, R^3 is a substituted or unsubstituted aryl carbonyl, a substituted or unsubstituted alkyl carbonyl, substituted or unsubstituted aryl alkyl carbonyl.

In another embodiment, R^4 is hydrogen, a cyano group, a substituted or unsubstituted alkyl group, or a substituted or unsubstituted alkoxy group. In a further embodiment, R^5 is hydrogen, a substituted or unsubstituted alkyl group or a halogen. R^4 and R^5 may be substituted with any of the substituents described herein, such that the compound of formula (I) is capable of performing its intended function, *e.g.*, modulate the sphingosine 1-phosphate receptor.

In yet another further embodiment, Q is –NH-CO- or –CO-NH-. In yet another further embodiment, Q is a substituted or unsubstituted aryl group, *e.g.*, phenyl or heteroaryl. Examples of heteroaryl Q groups include pyridyl, indolyl, imidazolyl, furanyl, and other N, S, and O containing heteroaryls.

In another embodiment, Q is a carbonyl or thiocarbonyl group.

In another embodiment, Q is CH_2NR-, -$CH_2NR(CO)$, -$NRSO_2$- or -SO_2-NR.

In another embodiment, R^6 is hydrogen, an alkoxy group, or an alkyl ether group. In another further embodiment, R^6 is a hydroxyl, substituted or unsubstituted alkyl group. R^6 may be substituted with any substituent which allows the resulting compound of formula (I) to perform its intended function. In another embodiment, R^6 is a

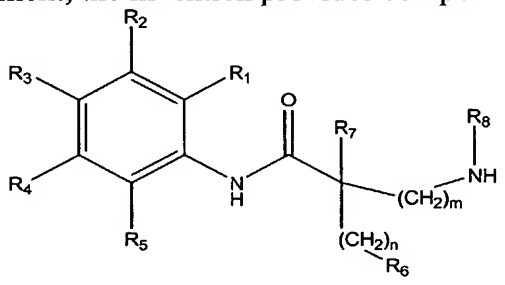
substituted or unsubstituted aryloxy group. Examples of substituted or unsubstituted R^6 aryloxy group include substituted or unsubstituted phenoxy group. These phenoxy groups may further be substituted with, for example, one or more substituted or unsubstituted alkyl groups.

In yet another embodiment, R^6 is a phosphate, alkyl phosphate, cycloalkyl phosphate, phosphonate, thiophosphate, alkylthiophosphate, cycloalkylthiophosphate, or thiophosphonate. Other examples of R^6 include carboxylic acids and substituted and unsubstituted alkyl esters and aryl esters.

In yet another further embodiment, R^7 is hydrogen, or a substituted or unsubstituted alkyl group. Examples of substituents for alkyl R^7 groups include hydroxy groups.

In yet another further embodiment, R^8 is hydrogen, hydroxyl, or substituted or unsubstituted alkyl.

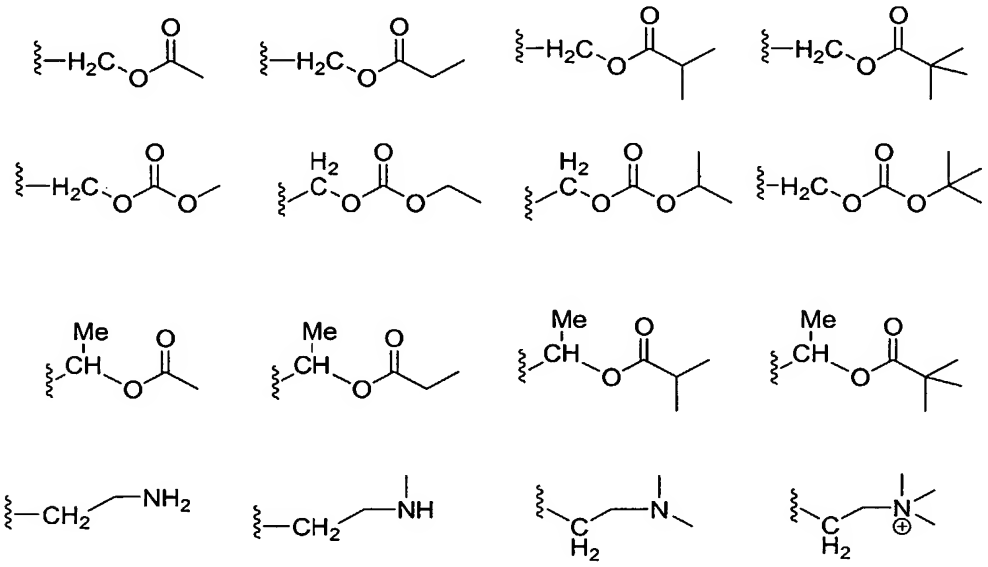
In one embodiment, the invention provides compounds of Formula II:



(II).

In a first set of compounds of Formula II, R_4 is C_4-C_{20}-alkoxy or an oxaalkyl, thiaalkyl or azaalkyl group having a chain length of from 4 to 20 atoms; a phenyl or substituted phenyl group, a phenoxy or substituted phenoxy group, a substituted or unsubstituted arylalkyl group, a substituted or unsubstituted arylalkoxy group, a substituted or unsubstituted heteroarylalkyl group; or a substituted or unsubstituted heteroarylalkoxy group. R_1, R_2, R_3 and R_5 are each independently selected from the group consisting of hydrogen, halogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 and N(R)R', wherein R and R' are each independently hydrogen, halogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-

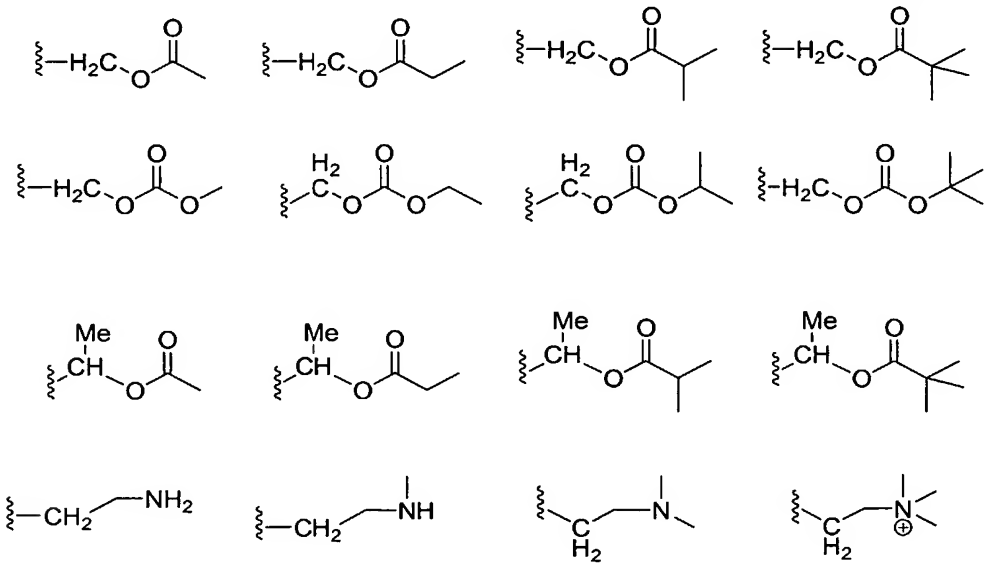
C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2. R^6 is –OH, $-CO_2R^9$, $-CH_2=CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R^{10} and R^{11} are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



R_7 is H, C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl or aryl. R_8 is H or C_1-C_6-alkyl. R_7 and R_8 can also together form a C_2-C_5-alkylene or a C_2-C_5-alkenylene group; m and n are each, independently, an integer from 0 to 3; provided that when R^4 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^3 and R^5 is not hydrogen; and when R^3 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^4 and R^5 is not hydrogen; and pharmaceutically acceptable salts thereof.

In a second set of compounds of Formula II, R_3 is C_4-C_{20}-alkoxy or an oxaalkyl, thiaalkyl or azaalkyl group having a chain length of from 4 to 20 atoms; a phenyl or substituted phenyl group, a phenoxy or substituted phenoxy group, a substituted or unsubstituted arylalkyl group, a substituted or unsubstituted arylalkoxy group, a substituted or unsubstituted heteroarylalkyl group; or a substituted or unsubstituted heteroarylalkoxy group. R_1, R_2, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight

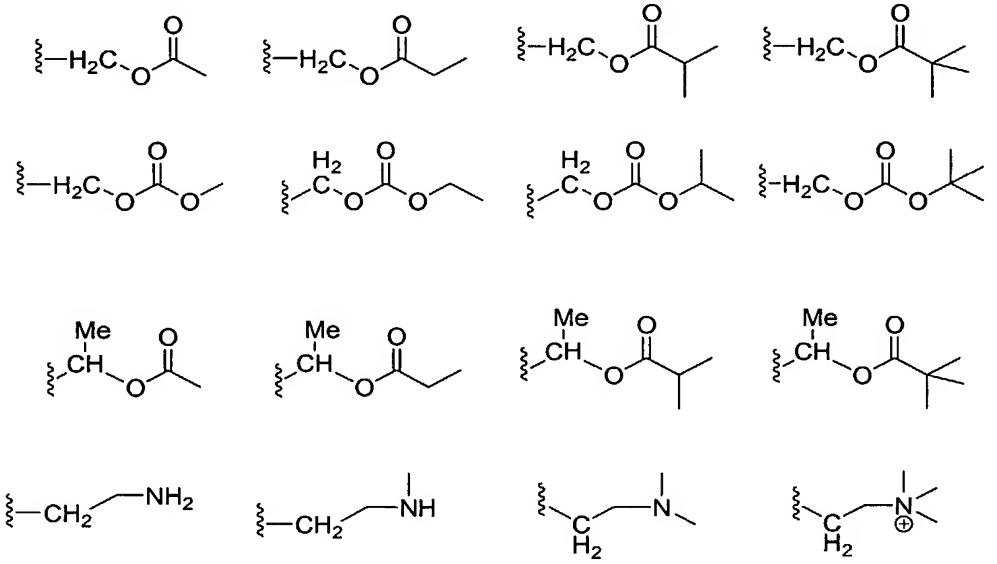
chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', wherein R and R' are each independently hydrogen, halogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2. R^6 is –OH, $-CO_2R^9$, $-CH_2{=}CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R^{10} and R^{11} are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



R_7 is H, C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl or aryl. R_8 is H or C_1-C_6-alkyl. R_7 and R_8 can also together form a C_2-C_5-alkylene or a C_2-C_5-alkenylene group; m and n are each, independently, an integer from 0 to 3, provided that when R^4 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^3 and R^5 is not hydrogen; and when R^3 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^4 and R^5 is not hydrogen; and pharmaceutically acceptable salts thereof.

In a third set of compounds of Formula II, R_3 is C_4-C_{20}-alkyl and R_1, R_2, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-

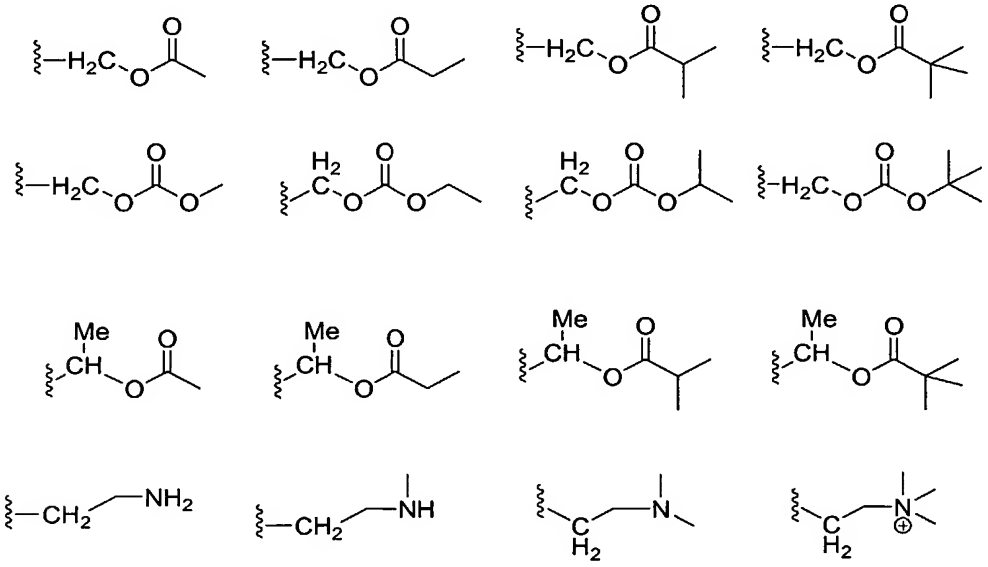
C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', wherein R and R' are each independently hydrogen, halogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2, provided that at least one of R_1, R_2, R_4 and R_5 is not hydrogen. R^6 is –OH, $-CO_2R^9$, $-CH_2{=}CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R^{10} and R^{11} are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



R_7 is H, C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl or aryl. R_8 is H or C_1-C_6-alkyl. R_7 and R_8 can also together form a C_2-C_5-alkylene or a C_2-C_5-alkenylene group; m and n are each, independently, an integer from 0 to 3; provided that when R^4 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^3 and R^5 is not hydrogen; and when R^3 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^4 and R^5 is not hydrogen; and pharmaceutically acceptable salts thereof.

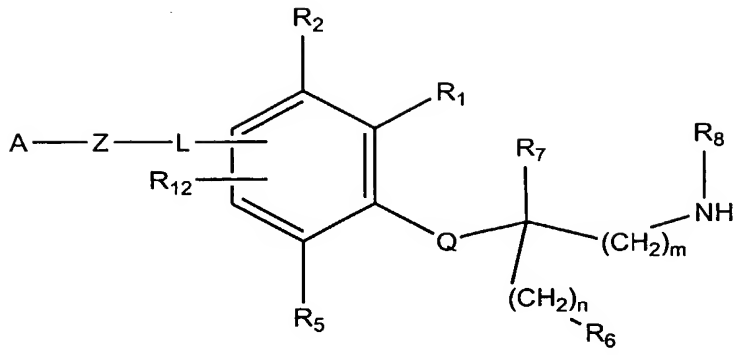
In a fourth set of compounds of Formula II, R_4 is C_4-C_{20}-alkyl; R_1, R_2, R_3 and R_5 are each independently selected from the group consisting of hydrogen, halogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or

branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', wherein R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2, provided that at least one of R_1, R_2, R_3 and R_5 is not hydrogen. R^6 is –OH, $-CO_2R^9$, $-CH_2{=}CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group R^{10} and R^{11} are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



R_7 is H, C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl or aryl. R_8 is H or C_1-C_6-alkyl. R_7 and R_8 can also together form a C_2-C_5-alkylene or a C_2-C_5-alkenylene group; m and n are each, independently, an integer from 0 to 3; provided that when R^4 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^3 and R^5 is not hydrogen; and when R^3 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^4 and R^5 is not hydrogen; and pharmaceutically acceptable salts thereof;

A preferred subset of compounds of the invention are the compounds of Formula IV:



(IV)

wherein:

L is alkoxy, a covalent bond, substituted or unsubstituted alkyl, alkylcarbonyl, thioether, alkylsulfonyl, alkylcarbonylamino, alkylaminocarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, or substituted or unsubstituted heteroaryl;

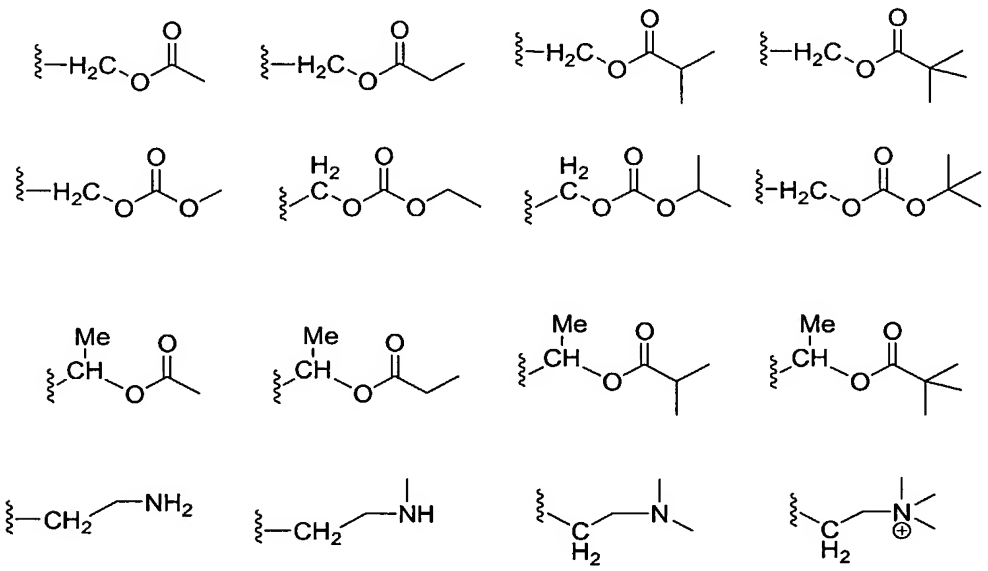
Z and A are each independently substituted or unsubstituted aryl, wherein Z and A may be linked by a covalent bond, substituted or unsubstituted alkyl, NH, alkyloxy, O, thioether, S, aminocarbonyl, carbonylamino, carbonyloxy, or oxycarbonyl;

R^1, R^2, R^5 and R^{12} are each independently selected from the group consisting of hydrogen, halogen, cyano, substituted or unsubstituted aryl, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', wherein R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2;

Q is $-CH_2NR-$, $-CH_2NR(CO)-$, $-NH(CO)-$, $-(CO)NH-$, $-(CO)-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NRSO_2-$, $-SO_2-NR-$ or heteroaryl, where R is hydrogen or straight chain or branched C_1-C_6-alkyl;

R^6 is $-OH$, $-CO_2R^9$, $-CH_2=CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R^{10} and R^{11} are each independently H,

straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



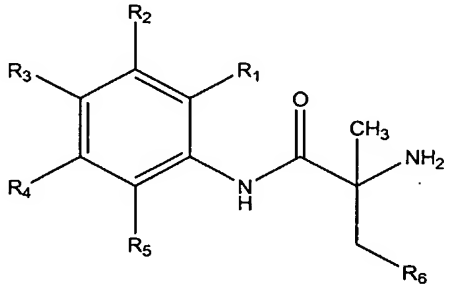
R^7 is H, C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, aryl, or together with R8 form a C_2-C_5-alkylene or a C_2-C_5-alkenylene group;

R^8 is H or C_1-C_6-alkyl; and

m and n are each, independently, an integer from 0 to 3;

provided that when R^4 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^3 and R^5 is not hydrogen; and when R^3 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^4 and R^5 is not hydrogen; and pharmaceutically acceptable salts thereof.

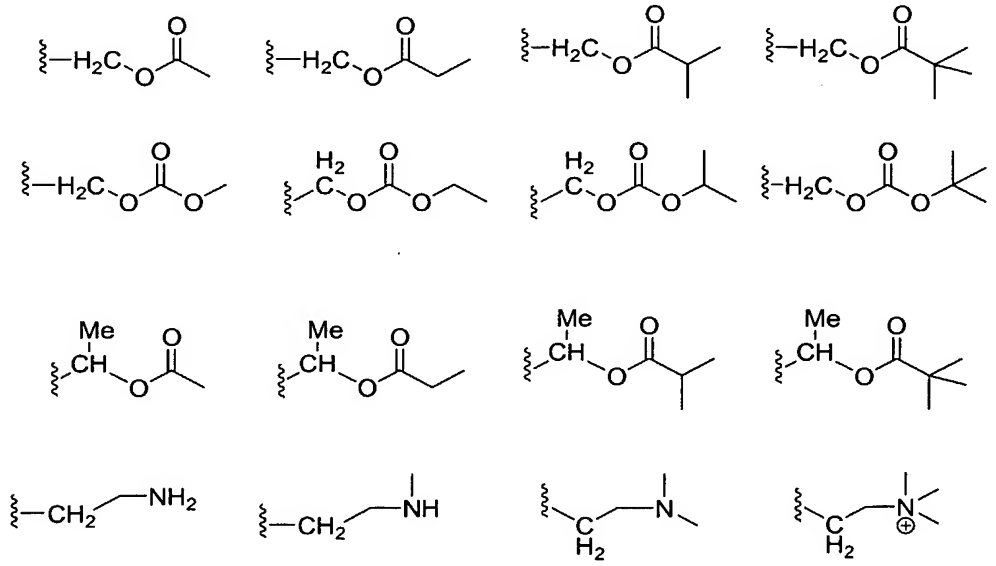
In yet another embodiment, the present invention provides compounds of Formula V:



(V)

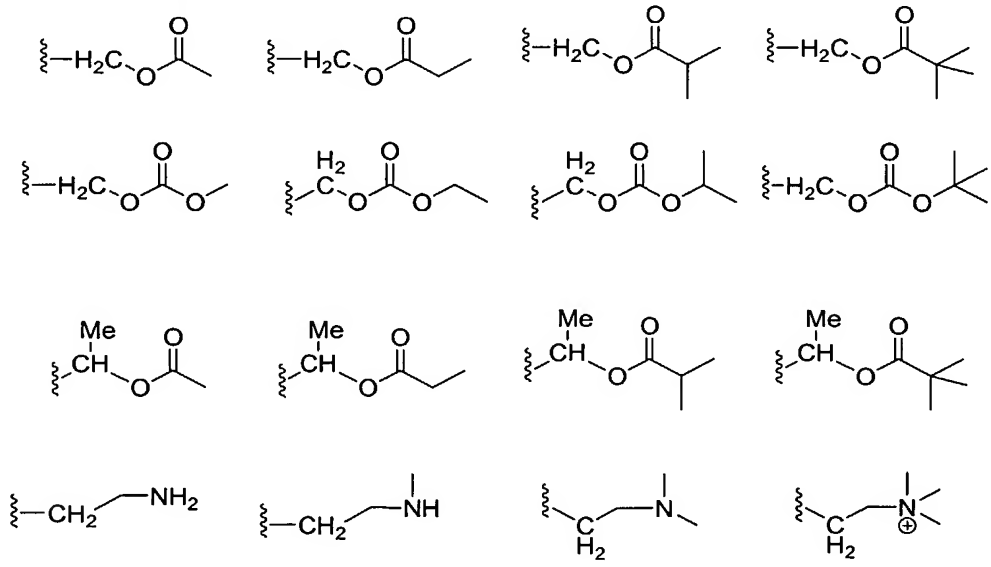
In a first set of compounds of Formula V, R_3 is C_6-C_{12}-alkoxy or an oxaalkyl, thiaalkyl or azaalkyl group having a chain length of from 6 to 12 atoms; a phenyl or C1-C6-aalkylphenyl group, a phenoxy or C1-C6-alkylphenoxy group, a substituted or

unsubstituted arylalkyl group, a substituted or unsubstituted arylalkoxy group, a substituted or unsubstituted heteroarylalkyl group; or a substituted or unsubstituted heteroarylalkoxy group. R_1, R_2, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 and N(R)R', wherein R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2. R^6 is –OH, $-CO_2R^9$, $-CH_2{=}CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R^{10} and R^{11} are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



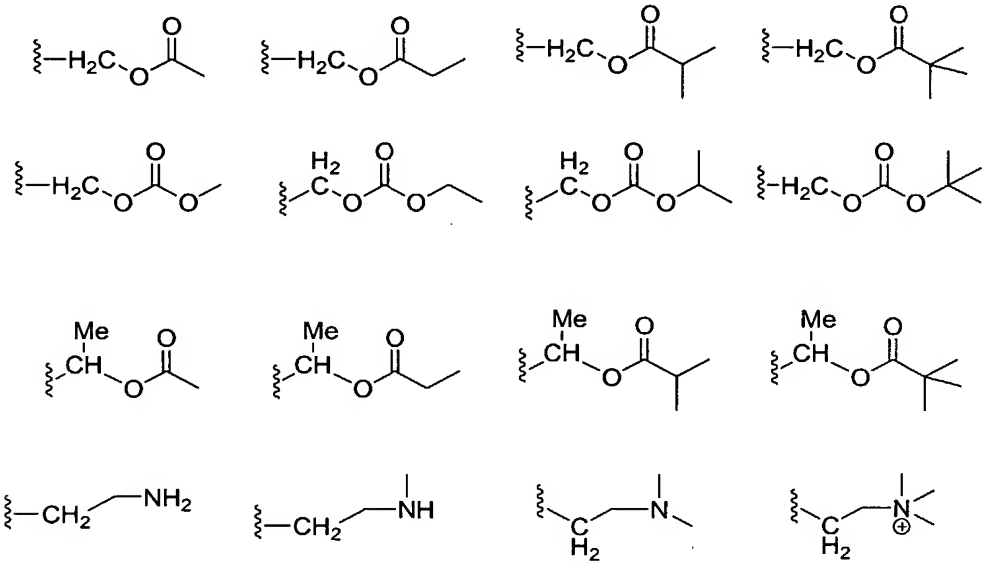
In a second set of compounds of Formula V, R_4 is C_6-C_{12}-alkoxy or an oxaalkyl, thiaalkyl or azaalkyl group having a chain length of from 6 to 12 atoms; a phenyl or C1-C6-aalkylphenyl group, a phenoxy or C1-C6-alkylphenoxy group, a substituted or unsubstituted arylalkyl group, a substituted or unsubstituted arylalkoxy group, a

substituted or unsubstituted heteroarylalkyl group; or a substituted or unsubstituted heteroarylalkoxy group. R_1, R_2, R_3 and R_5 are each independently selected from the group consisting of hydrogen, halogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', wherein R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2. R^6 is –OH, $-CO_2R^9$, $-CH_2{=}CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R^{10} and R^{11} are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



In a third set of compounds of Formula V, R_3 is C_6-C_{12}-alkyl; R_1, R_2, R_4 and R_5 are each independently selected from the group consisting of hydrogen, halogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R',

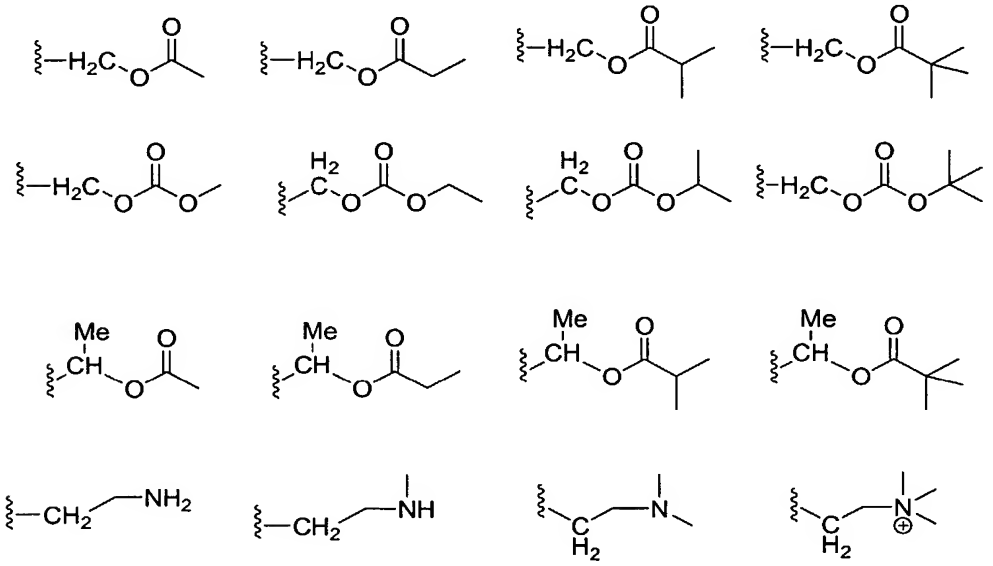
wherein R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2, and at least one of R_1, R_2, R_4 and R_5 is not hydrogen. R^6 is –OH, $-CO_2R^9$, $-CH_2{=}CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R^{10} and R^{11} are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



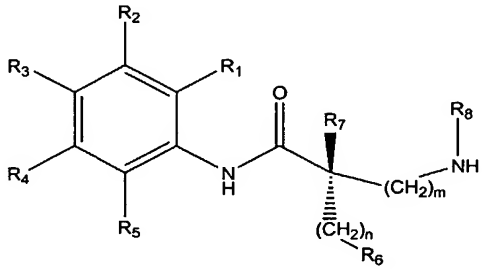
provided that when R^4 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^3 and R^5 is not hydrogen; and when R^3 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^4 and R^5 is not hydrogen; and pharmaceutically acceptable salts thereof.

In a fourth set of compounds of Formula V, R_4 is C_6-C_{12}-alkyl; R_1, R_2, R_3 and R_5 are each independently selected from the group consisting of hydrogen, halogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 and N(R)R', wherein R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-

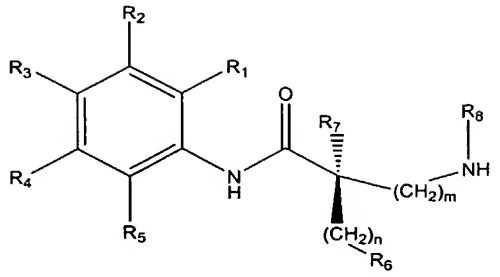
alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2, and at least one of R_1, R_2, R_3 and R_5 is not hydrogen. R^6 is –OH, $-CO_2R^9$, $-CH_2=CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R^{10} and R^{11} are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed in the below:



The compounds of Formula I can have the stereochemistry shown below as Formula V or Formula VI, wherein R_1-R_8 have the meanings given above for Formula I:



(V)



(VI)

In a first subset of compounds of Formula VI, R_4 is $CH_3(CH_2)_7$-O- or $CH_3(CH_2)_6$-O-; and R_1, R_2, R_3 and R_5 are independently selected from the group consisting of hydrogen, methyl, chloro, fluoro, and methoxy. In a preferred embodiment, at least one of R_1, R_2, R_3 and R_5 is not hydrogen.

In a second subset of compounds of Formula VI, R_3 is $CH_3(CH_2)_7$-O- or $CH_3(CH_2)_6$-O-; and R_1, R_2, R_4 and R_5 are independently selected from the group consisting of hydrogen, methyl, chloro, fluoro, trifluoromethyl and methoxy. In a preferred embodiment, at least one of R_1, R_2, R_4 and R_5 is not hydrogen.

In a third subset of compounds of Formula VI, R_4 is $CH_3(CH_2)_8$- or $CH_3(CH_2)_7$-; and R_1, R_2, R_3 and R_5 are independently selected from the group consisting of hydrogen, methyl, chloro, fluoro, trifluoromethyl, and methoxy, provided that at least one of R_1, R_2, R_3 and R_5 is not hydrogen.

In a fourth subset of compounds of Formula VI, R_3 is $CH_3(CH_2)_8$- or $CH_3(CH_2)_7$-; and R_1, R_2, R_4 and R_5 are independently selected from the group consisting of hydrogen, methyl, chloro, fluoro, trifluoromethyl and methoxy, provided that at least one of R_1, R_2, R_4 and R_5 is not hydrogen.

In a first subset of compounds of Formula VII, R_4 is $CH_3(CH_2)_7$-O- or $CH_3(CH_2)_6$-O-; and R_1, R_2, R_3 and R_5 are independently selected from the group consisting of hydrogen, methyl, chloro, fluoro, and methoxy. In a preferred embodiment, at least one of R_1, R_2, R_3 and R_5 is not hydrogen.

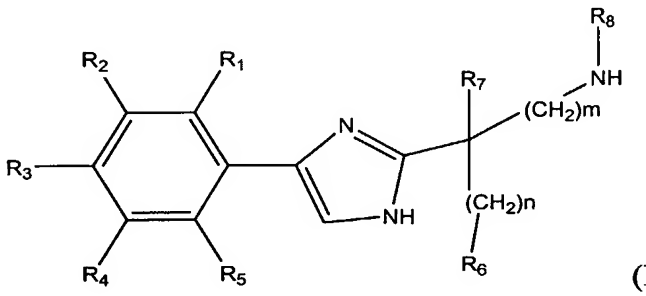
In a second subset of compounds of Formula VII, R_3 is $CH_3(CH_2)_7$-O- or $CH_3(CH_2)_6$-O-; and R_1, R_2, R_4 and R_5 are independently selected from the group consisting of hydrogen, methyl, chloro, fluoro, trifluoromethyl and methoxy. In a preferred embodiment, at least one of R_1, R_2, R_4 and R_5 is not hydrogen.

In a third subset of compounds of Formula VIII, R_4 is $CH_3(CH_2)_8$- or $CH_3(CH_2)_7$-; and R_1, R_2, R_3 and R_5 are independently selected from the group consisting of hydrogen, methyl, chloro, fluoro, trifluoromethyl, and methoxy, provided that at least one of R_1, R_2, R_3 and R_5 is not hydrogen.

In a fourth subset of compounds of Formula VIII, R_3 is $CH_3(CH_2)_8$- or $CH_3(CH_2)_7$-; and R_1, R_2, R_4 and R_5 are independently selected from the group consisting

of hydrogen, methyl, chloro, fluoro, trifluoromethyl and methoxy, provided that at least one of R_1, R_2, R_4 and R_5 is not hydrogen.

A preferred subset of compounds of Formula III includes compounds of Formula IX:



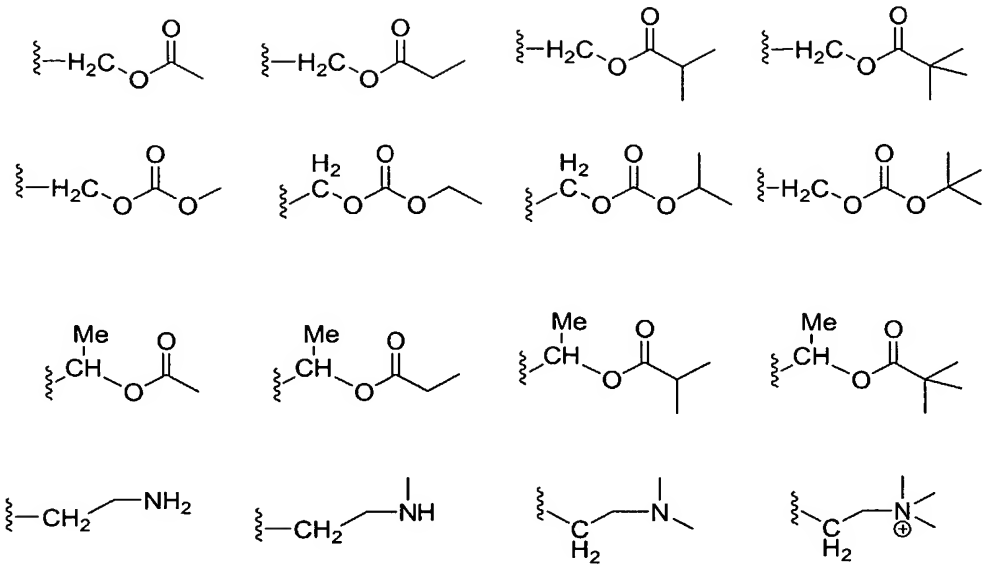
(IX),

wherein:

R_3 and R_4 are each independently C_6-C_{12}-alkoxy or an oxaalkyl, thiaalkyl or azaalkyl group having a chain length of from 6 to 12 atoms; a phenyl or C_1-C_6-alkylphenyl group, a phenoxy or C_1-C_6-alkylphenoxy group, a substituted or unsubstituted arylalkyl group, a substituted or unsubstituted arylalkoxy group, a substituted or unsubstituted heteroarylalkyl group; or a substituted or unsubstituted heteroarylalkoxy group;

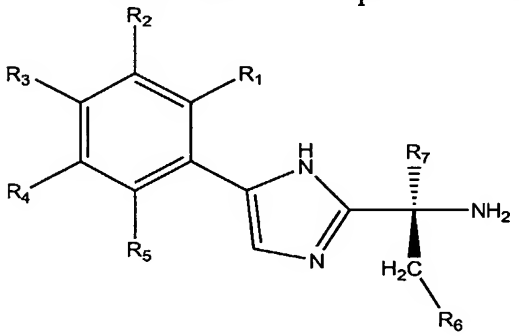
R_1, R_2, and R_5 are each independently selected from the group consisting of hydrogen, halogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 and N(R)R', wherein R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2;

R^6 is –OH, $-CO_2R^9$, $-CH_2=CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R^{10} and R^{11} are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:

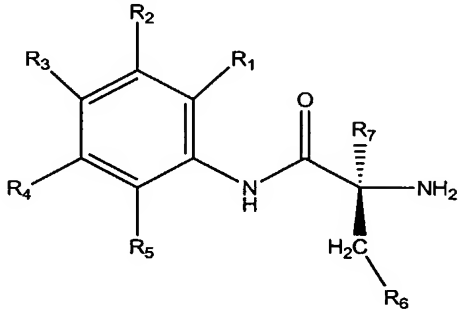


provided that when R^4 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^3 and R^5 is not hydrogen; and when R^3 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^4 and R^5 is not hydrogen; and pharmaceutically acceptable salts thereof;

The invention also provides compounds of Formula X or Formula XI:



X



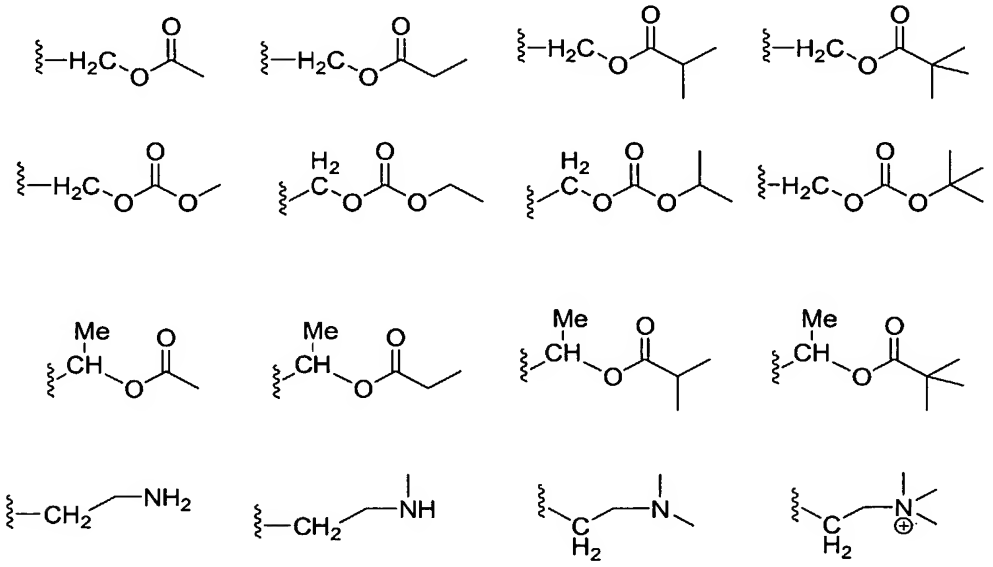
XI

wherein:

R_3 and R_4 are selected from the group consisting of optionally substituted C_6-C_{10}-alkoxy, optionally substituted aryl-C_1-C_6-alkoxy, optionally substituted heteroaryl-C_1-C_6-alkoxy, optionally substituted cycloalkyl-C_1-C_6-alkoxy, optionally substituted aryl-C_1-C_6-alkyl, optionally substituted heteroaryl-C_1-C_6-alkyl, optionally substituted cycloalkyl-C_1-C_6-alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aryloxy and optionally substituted heteroaryloxy;

R_1, R_2, and R_5 are each independently selected from the group consisting of halogen, trifluoromethyl, C_1-C_6-alkyl, and C_1-C_6-alkoxy;

R_7 is a C_1-C_6-alkyl group, preferably methyl; and R^6 is –OH, $-CO_2R^9$, $-CH_2=CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R^{10} and R^{11} are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:

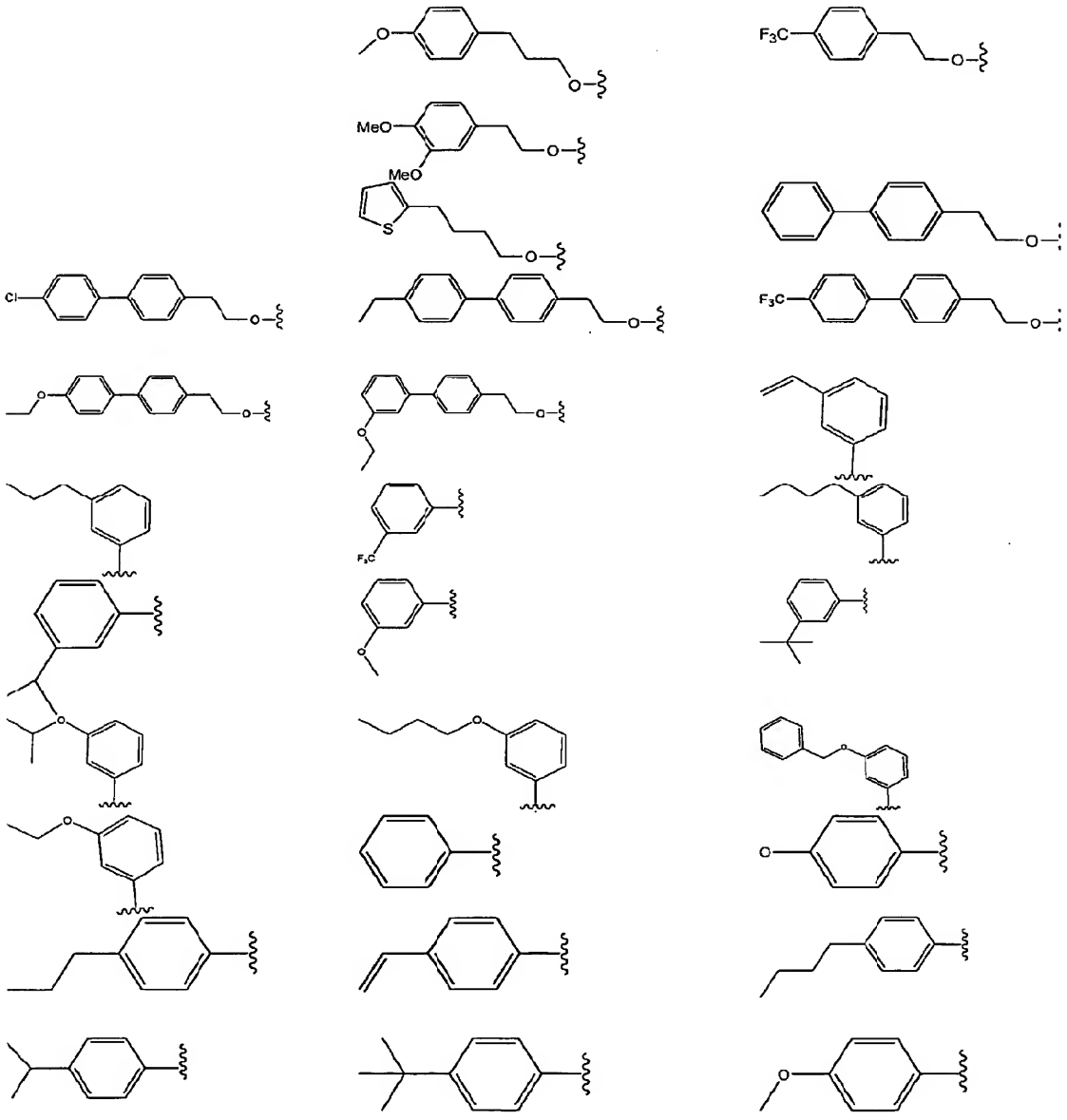


and pharmaceutically acceptable salts, esters and prodrugs thereof.

R_3 and R_4 are preferably biphenyl-C_1-C_4-alkoxy, where the biphenyl group optionally includes one or more substituents selected from C_1-C_4-alkyl, C_1-C_4-alkenyl, C_1-C_4-alkoxy, cyano, halogen and trifluoromethyl; phenyl-C_1-C_4-alkoxy, wherein the phenyl group optionally includes one or more substituents selected from C_1-C_4-alkyl, C_1-C_4-alkenyl, C_1-C_4-alkoxy, cyano, halogen, methylenedioxy, and trifluoromethyl; naphthyl-C_1-C_4-alkoxy, wherein the naphthyl group optionally includes one or more substituents selected from C_1-C_4-alkyl, C_1-C_4-alkenyl, C_1-C_4-alkoxy, cyano, halogen and trifluoromethyl; C_5-C_8-cycloalkyl-C_1-C_4-alkoxy; heteroaryl-C_1-C_4-alkoxy, wherein the heteroaryl group is imidazolyl; 2-, 3- or 4-pyridyl; or thiophene, optionally substituted by one or more C_1-C_4-alkyl, C_1-C_4-alkenyl, C_1-C_4-alkoxy, cyano, halogen, benzyl, benzyloxy or trifluoromethyl groups; phenyl, optionally substituted by one or more C_1-C_4-alkyl, C_1-C_4-alkenyl, C_1-C_4-alkoxy, cyano, halogen, methylenedioxy, benzyl, benzyloxy or trifluoromethyl groups; naphthyl, optionally substituted by one or more C_1-C_4-alkyl, C_1-C_4-alkenyl, C_1-C_4-alkoxy, cyano, halogen, methylenedioxy, benzyl,

benzyloxy or trifluoromethyl groups; or heteroaryl, such as imidazolyl; 2-,3- or 4-pyridyl or thiophene; optionally substituted by one or more C_1-C_4-alkyl, C_1-C_4-alkenyl, C_1-C_4-alkoxy, cyano, halogen, benzyl, benzyloxy or trifluoromethyl groups.

In one set of compounds of Formulas X and XI, R_3 or R_4 is a group selected from, but not limited to, those shown below:



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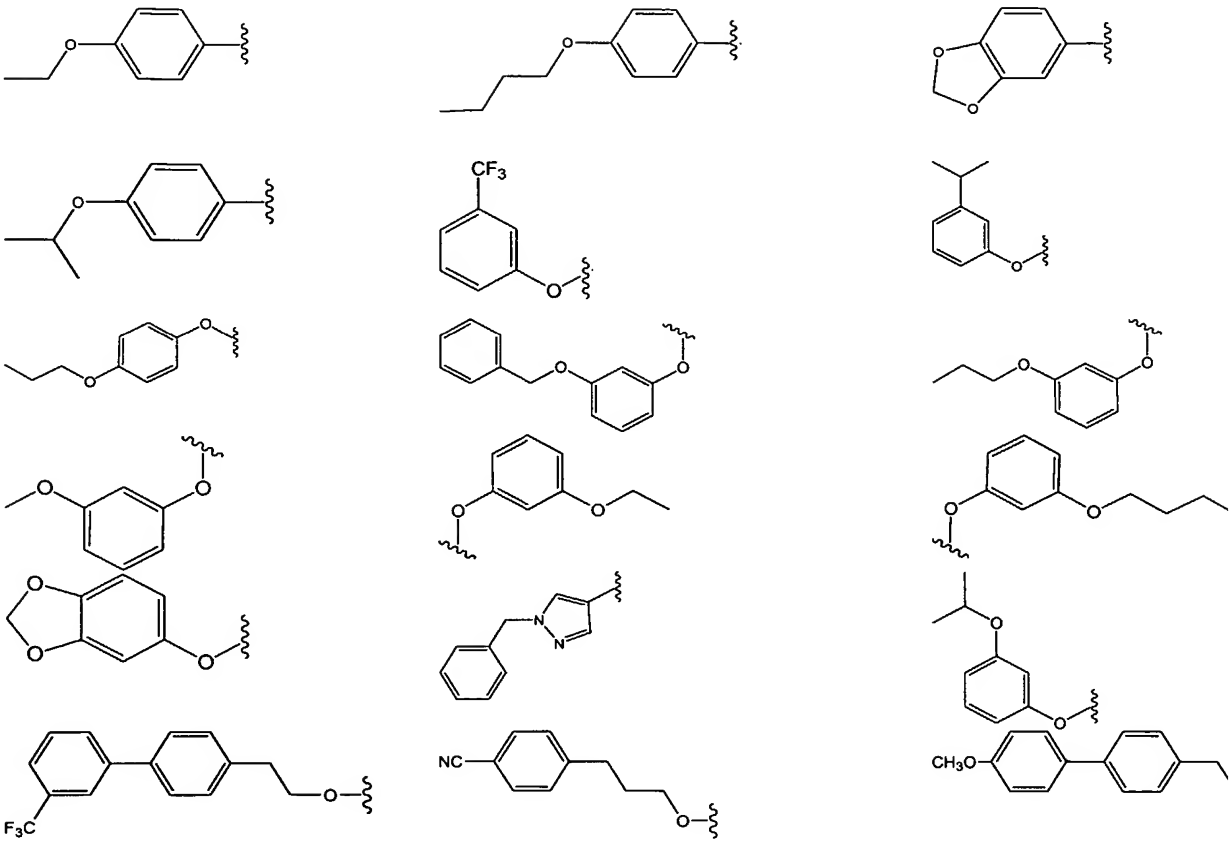
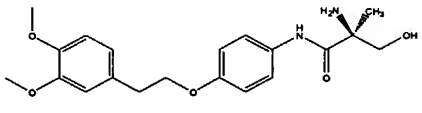


Specific compounds of the invention include, but are not limited to, those set forth below and their salts. While the compounds below are represented as alcohols (R_6 is hydroxy) or phosphates (R_6 is $-OPO_3H_2$), specific compounds of the invention further include derivatives of these compounds where R_6 is carboxylate, methylenephosphonate, thiophosphate hydroxymethylenephosphonate, fluoromethylenephosphonate.



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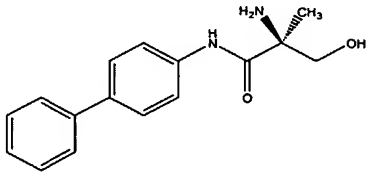

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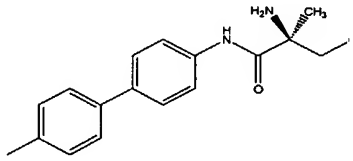

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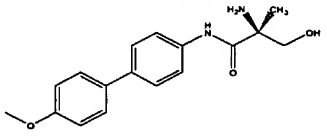

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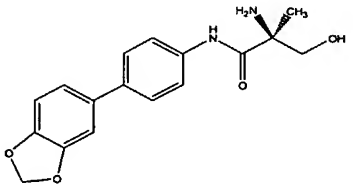

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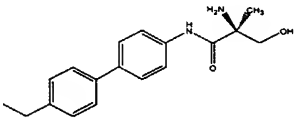

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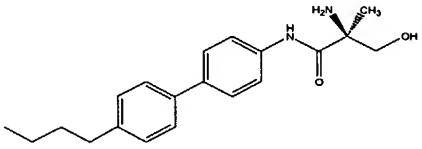

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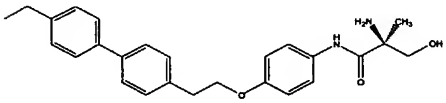

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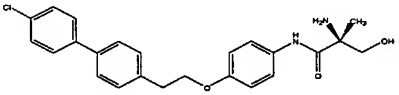

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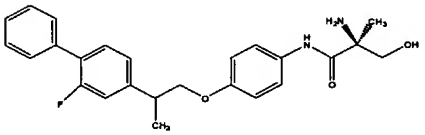

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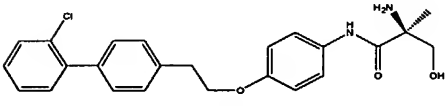

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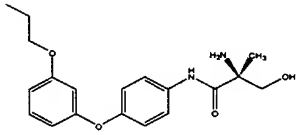

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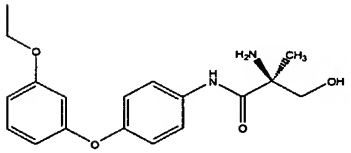

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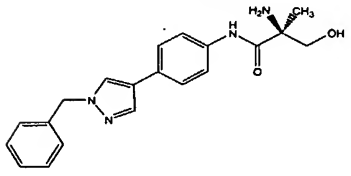

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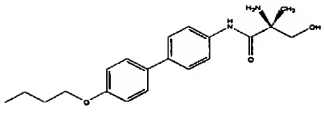

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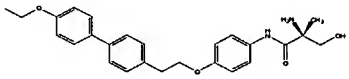

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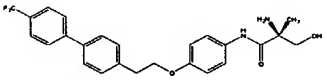

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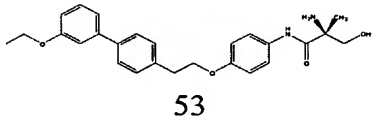

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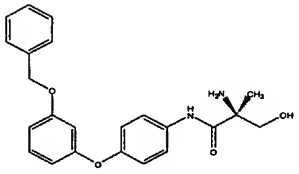

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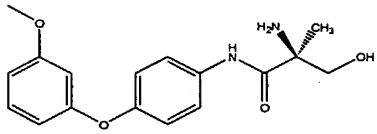

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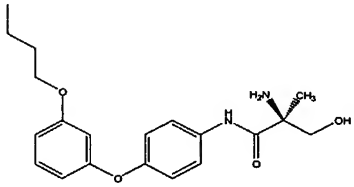

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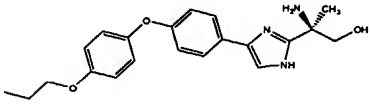

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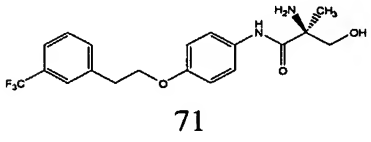

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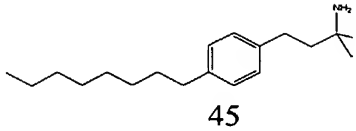

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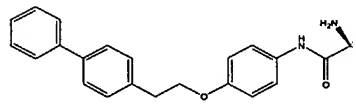

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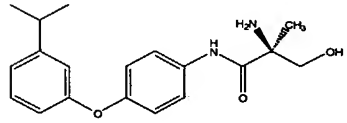

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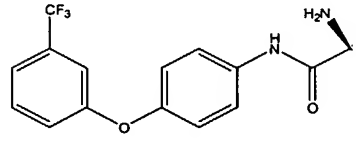

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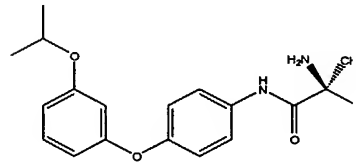

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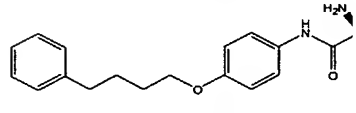

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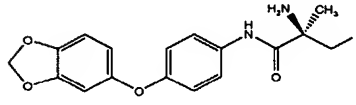

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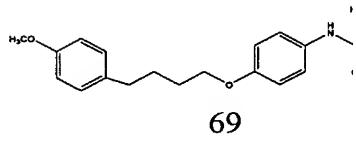

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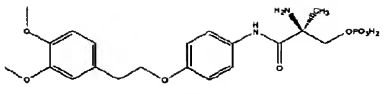
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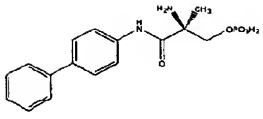
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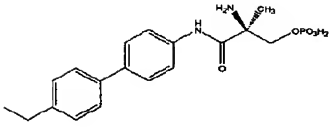
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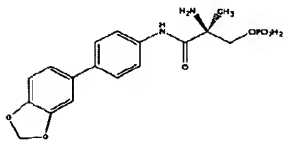
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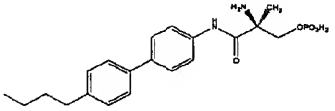
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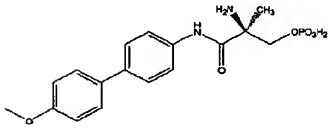
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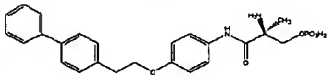
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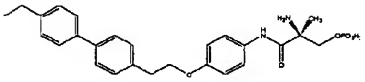
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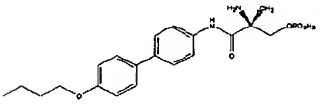
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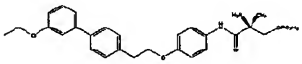
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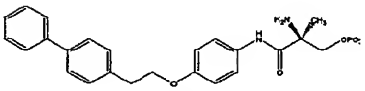
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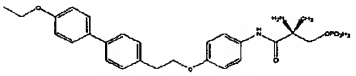
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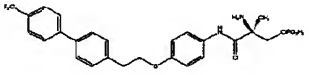
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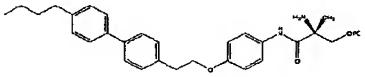
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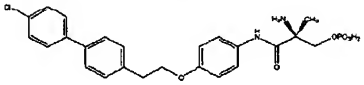
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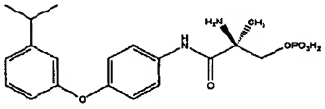
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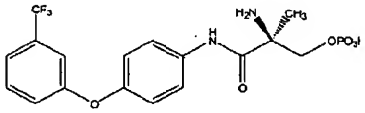
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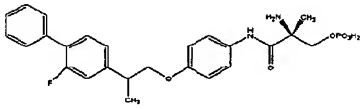
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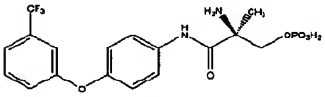
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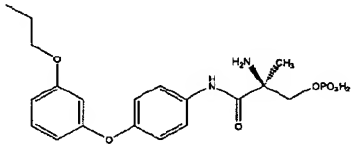
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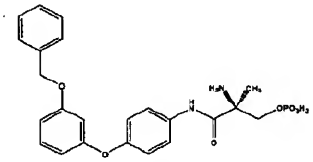
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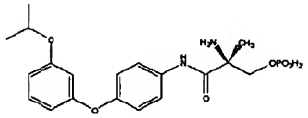
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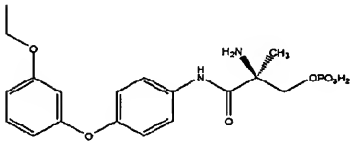
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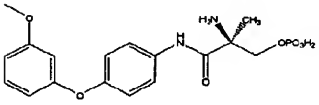
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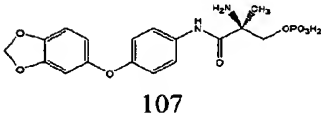
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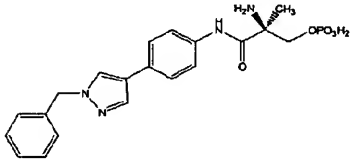
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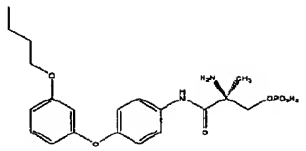

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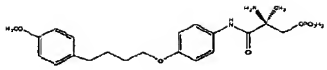

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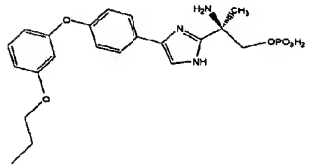

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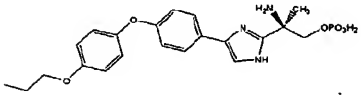

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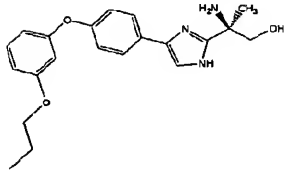

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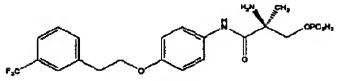

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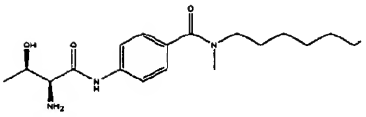

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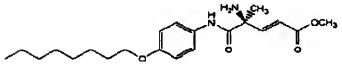

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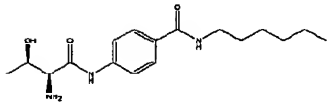

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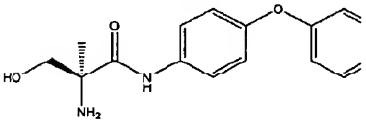

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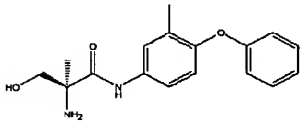

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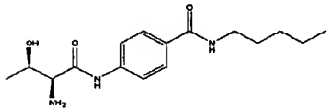

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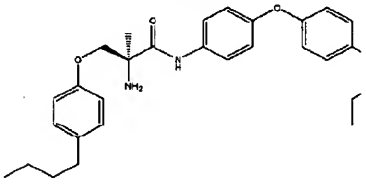

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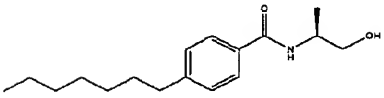

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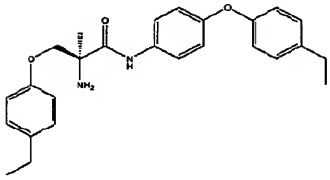

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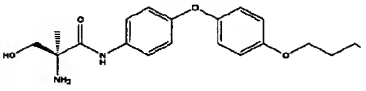

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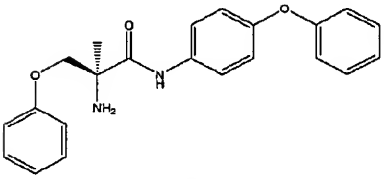

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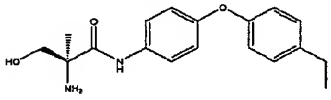

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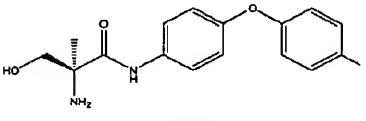

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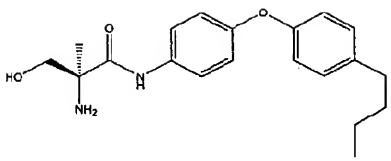

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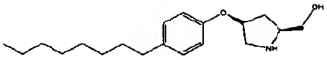

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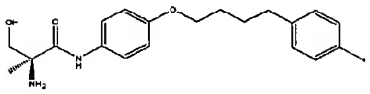

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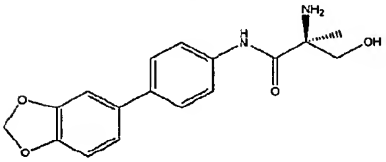

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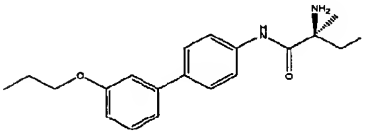

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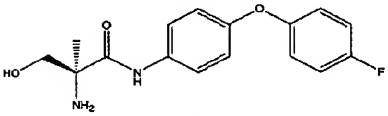

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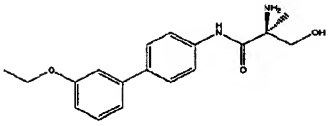

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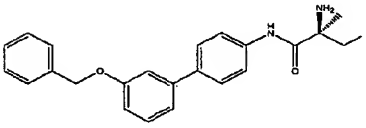

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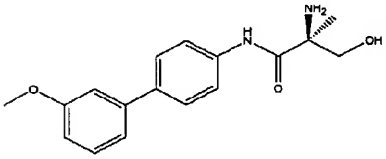

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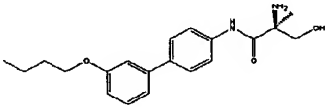

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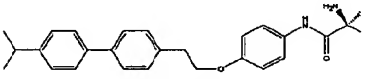

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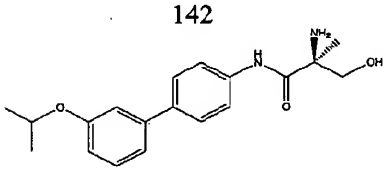

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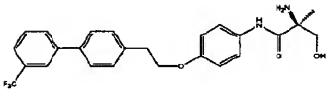

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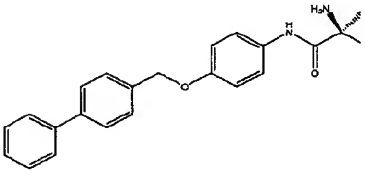

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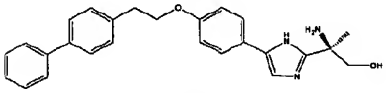

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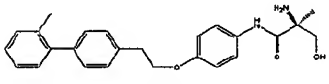

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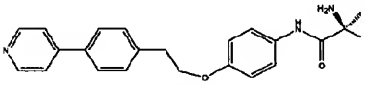

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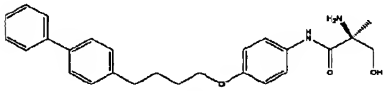

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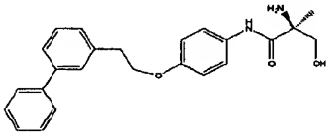

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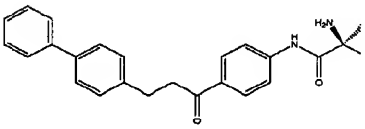

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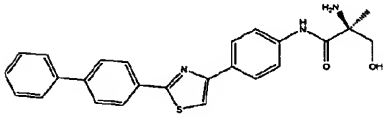

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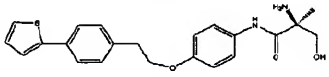

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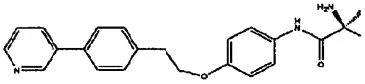

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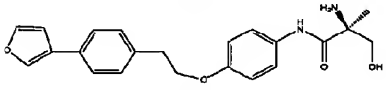

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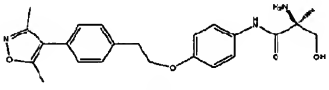

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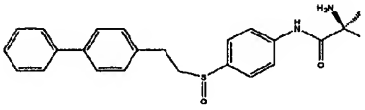

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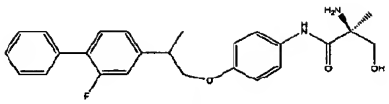

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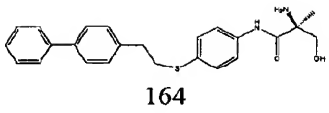

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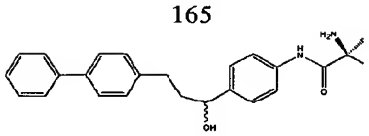

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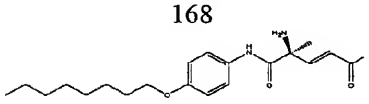

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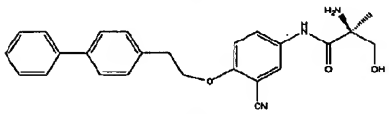

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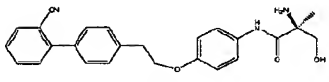

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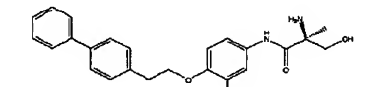

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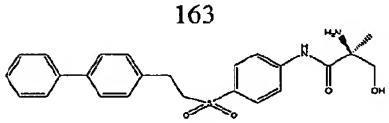

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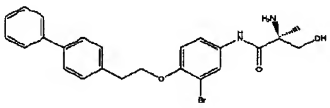

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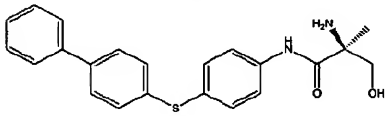

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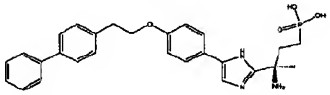

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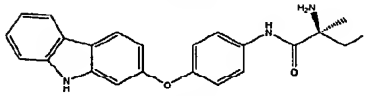

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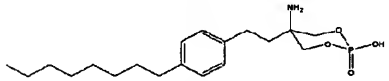

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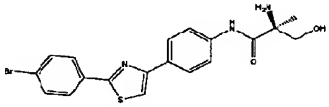

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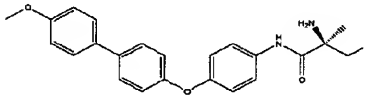

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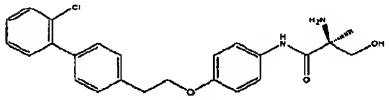

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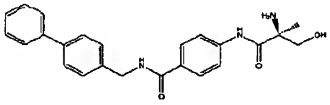

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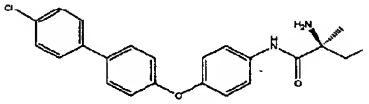

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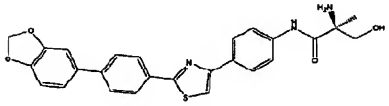

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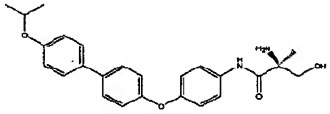

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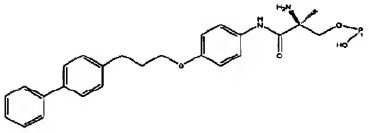

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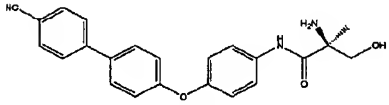

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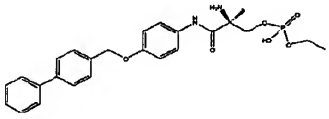

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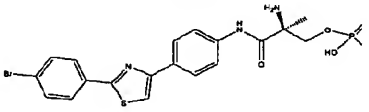

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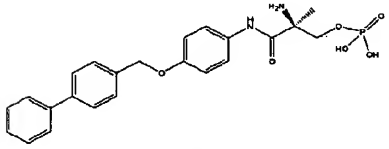

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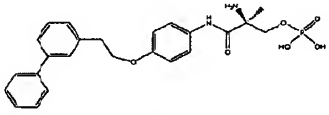

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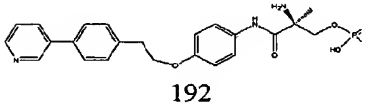

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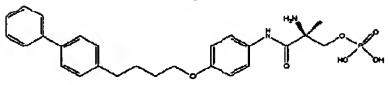

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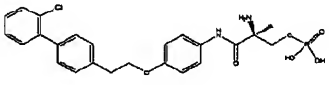

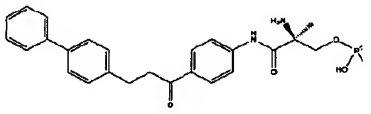

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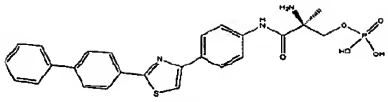

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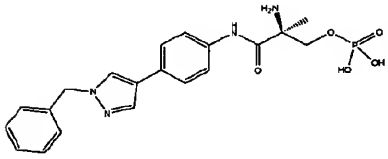

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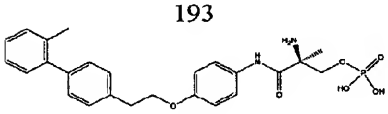

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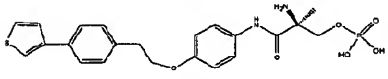

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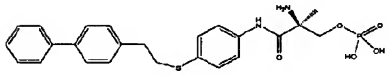

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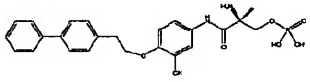

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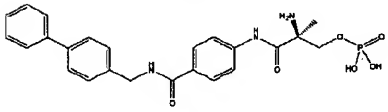

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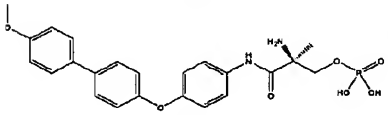

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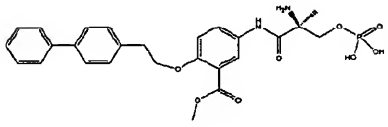

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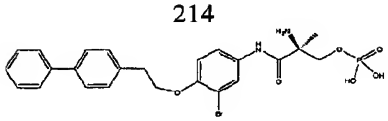

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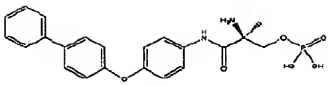

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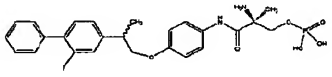

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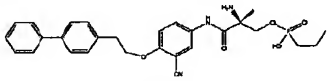

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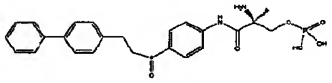

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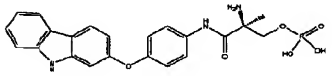

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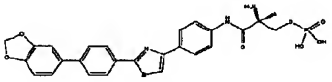

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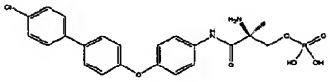

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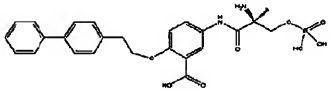

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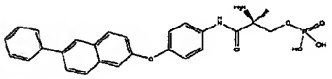

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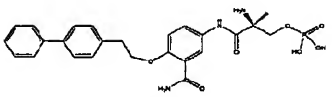

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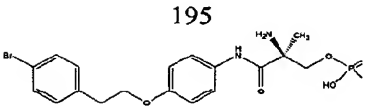

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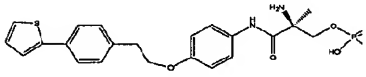

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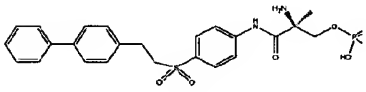

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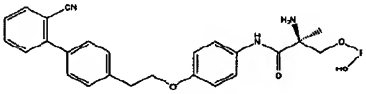

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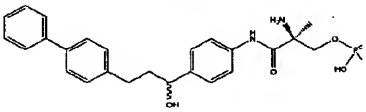

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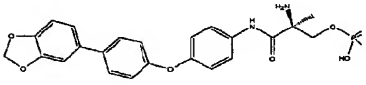

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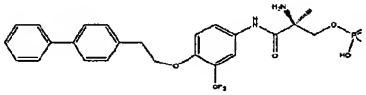

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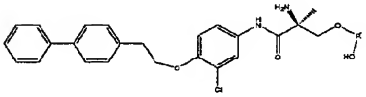

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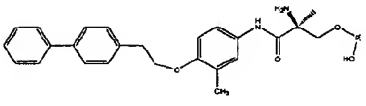

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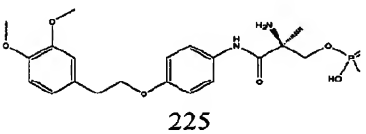

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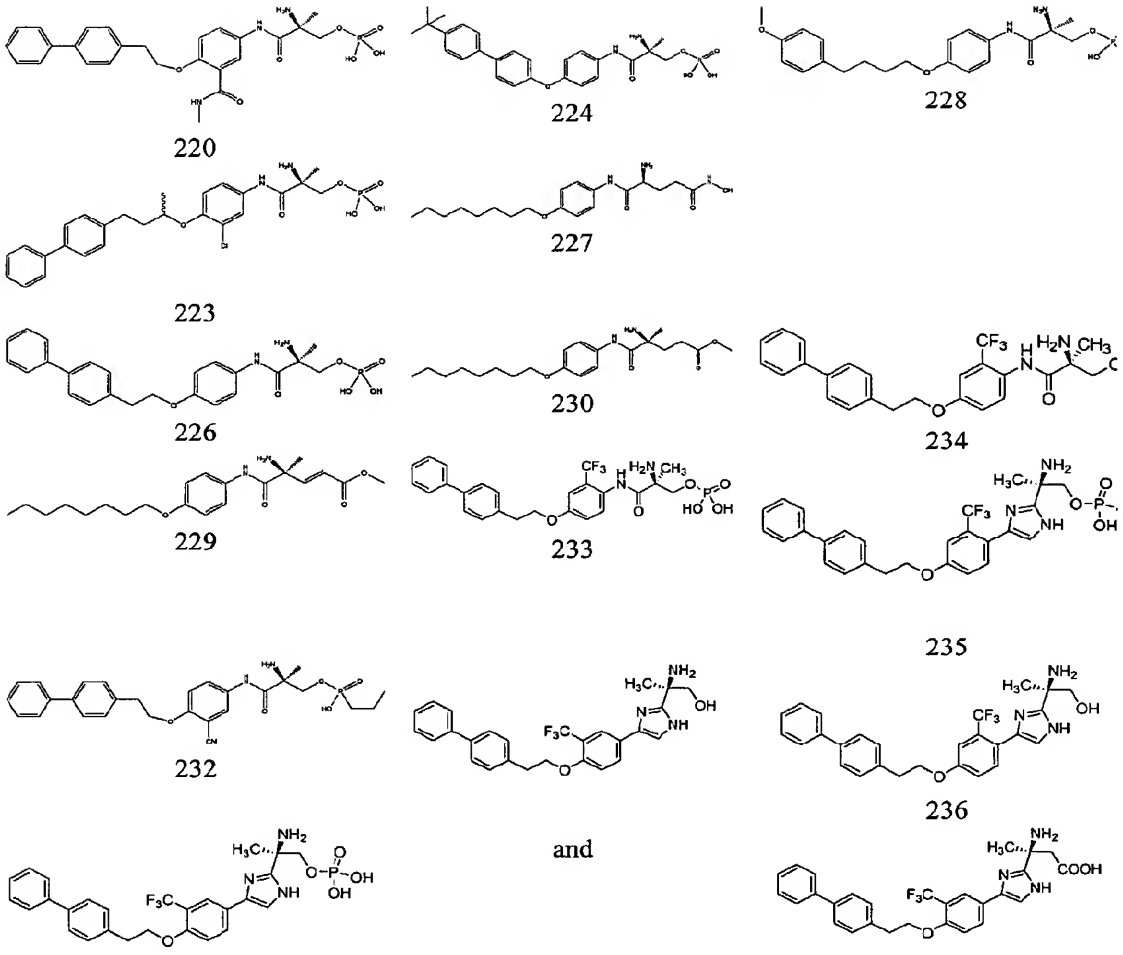


The invention also relates to salts of the compounds of the invention and, in particular, to pharmaceutically acceptable salts. A "pharmaceutically acceptable salt" includes a salt that retains the desired biological activity of the parent compound and does not impart any undesired toxicological effects. The salts can be, for example, salts with a suitable acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like; acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, benzoic acid, pamoic acid, alginic acid, methanesulfonic acid, naphthalenesulfonic acid, and the like. Also included are salts of cations such as ammonium, sodium, potassium, lithium, zinc, copper, barium, bismuth, calcium, and the like; or organic cations such as tetralkylammonium and trialkylammonium cations. Combinations of the above salts are also useful. Salts of other acids and/or cations are also included, such as salts with trifluoroacetic acid, chloroacetic acid, and trichloroacetic acid.

The invention also includes different crystal forms, hydrates and solvates of the compounds of the invention, as well as stereoisomers of the compounds of the invention. Included are substantially pure single stereoisomers and mixtures of stereoisomers.

In a further embodiment, the compound of Formula I is an agonist of a sphingosine 1-phosphate 1 receptor.

Preferred compounds of Formulas I, II IV and IX include compounds which are agonists of the S1P receptor. Particularly preferred are compounds which are selective for the S1P1 receptor compared to one or more of the other S1P receptors. For example, one set of preferred compounds includes compounds which are selective for the S1P1 receptor relative to the S1P3 receptor. Compounds selective for the S1P1 receptor can be agonists of the S1P1 receptor, significantly weaker agonists of one or more other receptors and/or antagonists of one or more other receptors. A compound is "selective" for the S1P1 receptor relative to a second receptor, if the IC_{50} of the compound for the second receptor is at least two-fold, preferably at least 10-fold, and more preferably at least 100-fold greater than the IC_{50} for the S1P1 receptor. The IC_{50} of a compound is determined using the ^{35}S-GTPγS binding assay, as described in WO 03/061567, the contents of which are incorporated herein by reference.

The terms "agonist" or "S1P1 receptor agonist" as used herein include the compounds described herein which bind to and/or agonize the S1P1 receptor. In one embodiment, the S1P receptor agonists have an IC_{50} for the S1P1 receptor of about 100 nM - 0.25 nM, about 50 nM – 0.25 nM, about 25 nM – 0.5 nM, about 100 nM or less, about 75 nM or less, about 50 nM or less, about 40 nM or less, about 30 nM or less, about 20 nM or less, about 10 nM or less, about 5 nM or less, about 1 nM or less, about 0.5 nM or less, or about 0.25 nM or less. The compounds' IC_{50} for the S1P1 receptor can be measured using the binding assays described in Example 11 or those described in WO 03/061567.

Ranges intermediate to the above recited values are also intended to be part of this invention. For example, ranges using a combination of any of the above recited values as upper and/or lower limits are intended to be included.

In a further embodiment, the S1P receptor agonist has an IC_{50} value for the S1P3 receptor of about 10 nM - 10,000 nM, about 100 nM – 5000 nM, about 100 nM – 3000 nM, about 10 nM or greater, about 20 nM or greater, about 40 nM or greater, about 50 nM or greater, about 75 nM or greater, or about 100 nM or greater. In another embodiment, the S1P compound of the invention binds the S1P3 receptor with an IC_{50} of 1000 nM or greater, 2000 nM or greater, 3000 nM or greater, 5000 nM or greater, 10,000 nM or greater. The IC_{50} for of S1P3 receptor can be measured using the binding assays described in Example 11 or those described in WO 03/061567.

Ranges intermediate to the above recited values are also intended to be part of this invention. For example, ranges using a combination of any of the above recited values as upper and/or lower limits are intended to be included.

In yet another embodiment, the S1P receptor agonists described herein have an IC_{50} value for the S1P1 receptor that is about 5-fold lower, about 10-fold lower, about 20-fold lower, about 50-fold lower, about 100-fold lower, about 200-fold lower, about 500-fold lower or about 1000-fold lower than their IC_{50} value for the S1P3 receptor.

Ranges intermediate to the above recited values are also intended to be part of this invention. For example, ranges using a combination of any of the above recited values as upper and/or lower limits are intended to be included.

In a further embodiment, when Q is NH(C=O), O, or heteroaryl; R^6 is OH; n is 1-4; one of R^1, R^2, R^3, R^4, and R^5 is C_1-C_{18} alkyl, C_2-C_{18} alkenyl, C_2-C_{18} alkynyl, C_5-C_{18}-alkoxy, $(CH_2)_{1-10}O(CH_2)_{1-10}$, C_5-C_{10}(aryl), C_5-C_{10}(aryl)(C_1-C_{10}alkyl), C_5-C_{10}(heteroaryl), C_5-C_{10}(heteroaryl)(C_1-C_{10}alkyl), C_5-C_{10} cycloalkyl, C_5-C_{10}(cycloalkyl)-(C_1-C_5 alkyl), C_5-C_{10}alkoxy(aryl), C_5-C_{10}alkoxy(aryl)(C_1-C_{10} alkyl), C_5-C_{10}alkoxy(heteroaryl), C_5-C_{10}alkoxy(heteroaryl)(C_1-C_{10} alkyl), C_5-C_{10}alkoxy(cycloalkyl), or C_5-C_{10}alkoxy(cycloalkyl)(C_1-C_{10} alkyl); and one of R^1, R^2, R^3, R^4, and R^5 is H, halogen, NH_2, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylamino, C_1-C_6 alkylcyano, or C_1-C_6 alkylthio, R^8 is not hydrogen.

In another further embodiment, when Q is heteroaryl; one of R^1, R^2, R^3, R^4, and R^5 is alkyl, alkenyl, alkynyl, optionally substituted aryl, optionally substituted heteroaryl, alkyl (optionally substituted aryl), arylalkyl, or arylalkyl (optionally substituted (aryl); R^8 is hydrogen; n is 1; R^6 is not OH.

In another further embodiment, when Q is NH(C=O); R^6 is OH; R^1, R^2, R^3, R^4, and R^5 are each independently halogen, hydrogen, amino, or alkyl; R^8 is not hydrogen.

In one embodiment, the compounds of the invention do not include the compounds described in WO 05/041899A2, WO 04/010949A2, WO 04/024673 A1 and WO 02/064616; the entire contents of each of which are hereby incorporated herein by reference.

Methods of Using the Compounds of the Invention

In a further embodiment, the invention pertains, at least in part to a method for treating a sphingosine 1-phosphate associated disorder in a subject. The method includes administering to a subject an S1P compound described herein in an amount effective for treating an S1P associated disorder.

The term "sphingosine 1-phosphate associated disorder" includes disorders, diseases or conditions which are associated with or caused by a misregulation in S1P receptor function and/or signalling or S1P receptor ligand funtion. The term also

includes diseases, disorders or conditions which can be treated by administering to a subject an effective amount of a sphingosine 1-phosphate receptor agonist. Such disorders include disorders that are associated with an inappropriate immune response and conditions associated with an overactive immune response.

In another embodiment, the present invention provides a method of treating a condition associated with an overactive immune response. An "overactive immune response" is an undesirable or inappropriate immune response and in conditions associated with an overactive immune response, the immune response is deleterious to the subject. Included are conditions such as autoimmune disorders, organ and tissue transplants, including transplant rejection and graft versus host disease, and chronic inflammatory disorders. The method includes administering to the subject a therapeutically effective amount of a compound of the present invention, thereby treating the condition associated with an overactive immune response in the subject.

The compounds of the invention can be used to treat subjects undergoing, or who have undergone, an organ, tissue or cell transplant from a donor. In one embodiment, the transplanted tissue, organ or cell is bone marrow, stem cells, pancreatic cells, such as islet cells, or cornea. In another embodiment, the transplanted organ is a solid organ, such as a liver, a kidney, a heart or a lung.

Autoimmune disorders which can be treated with the compounds of the invention include systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, type 1 diabetes, ankylosing spondylitis, psoriatic arthritis, scleroderma, Kawasaki syndrome and other rheumatic diseases as set forth in Primer on the Rheumatic Diseases, 11th Edition (John H. Klippel MD, editor; Arthritis Foundation:Atlanta Ga. (1997)).

Other autoimmune diseases that can be treated with the present compounds include active chronic hepatitis, Addison's Disease, anti-phospholipid syndrome, atopic allergy, autoimmune atrophic gastritis, achlorhydra autoimmune, Celiac Disease, Crohn's Disease, Cushing's Syndrome, dermatomyositis, Goodpasture's Syndrome, Grave's Disease, Hashimoto's thyroiditis, idiopathic adrenal atrophy, idiopathic thrombocytopenia, Lambert-Eaton Syndrome, lupoid hepatitis, mixed connective tissue disease, pemphigoid, pemphigus vulgaris, pernicious anemia, phacogenic uveitis, polyarteritis nodosa, primary biliary cirrhosis, primary sclerosing cholangitis, psoriasis, Raynauds, Reiter's Syndrome, relapsing polychondritis, Schmidt's Syndrome, Sjogren's Syndrome, sympathetic ophthalmia, Takayasu's Arteritis, temporal arteritis, thyrotoxicosis, Type B Insulin Resistance, ulcerative colitis, and Wegener's granulomatosis.

As used herein, the term "subject" includes warm-blooded animals, preferably mammals, including humans, cats, dogs, horses, bears, lions, tigers, ferrets, rabbits,

mice, cows, sheep, pigs, etc. In a preferred embodiment, the subject is a primate. In an even more preferred embodiment, the primate is a human.

As used herein, the term "administering" to a subject includes dispensing, delivering or applying a compound of the invention in a pharmaceutical formulation (as described herein), to a subject by any suitable route for delivery of the compound to the desired location in the subject, including delivery by either the parenteral or oral route, intramuscular injection, subcutaneous/intradermal injection, intravenous injection, buccal administration, topical delivery, transdermal delivery and administration by the rectal, colonic, vaginal, intranasal or respiratory tract route.

As used herein, the term "effective amount" includes an amount effective, at dosages and for periods of time necessary, to achieve the desired result, *e.g.*, sufficient to treat the condition in a subject. An effective amount of a compound of the invention, as defined herein, may vary according to factors such as the disease state, age, and weight of the subject, and the ability of the compound to elicit a desired response in the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response. An effective amount is also one in which any toxic or detrimental effects (*e.g.*, side effects) of the compound are outweighed by the therapeutically beneficial effects.

A therapeutically effective amount of a compound of the invention (i.e., an effective dosage) may range from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight. The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a compound of the invention can include a single treatment or, preferably, can include a series of treatments. It will also be appreciated that the effective dosage of the compound used for treatment may increase or decrease over the course of a particular treatment.

The methods of the invention further include administering to a subject a therapeutically effective amount of a compound of the invention in combination with another pharmaceutically active compound known to treat the disease or condition, *e.g.*, an immunomodulatory agent or an anti-inflammatory agent. Pharmaceutically active compounds that may be used depend upon the condition to be treated, but include as examples cyclosporin, rapamycin, FK506, methotrexate, etanercept, infliximab, adalimumab, non-steroidal anti-inflammatory agents, cyclooxygenase-2-inhibitors, such as celecoxib and rofecoxib, and corticosteroids. Other suitable compounds can be found in Harrison's Principles of Internal Medicine, Thirteenth Edition, Eds. T. R. Harrison et al. McGraw-Hill N.Y., N.Y.; and the Physicians Desk Reference 50th Edition 1997,

Oradell New Jersey, Medical Economics Co., the complete contents of which are expressly incorporated herein by reference. The compound of the invention and the additional pharmaceutically active compound may be administered to the subject in the same pharmaceutical composition or in different pharmaceutical compositions (at the same time or at different times).

Pharmaceutical Compositions of the Compounds of the Invention

The present invention also provides pharmaceutically acceptable formulations and compositions comprising one or more compounds of the invention, *e.g.*, compounds of Formula I or compounds otherwise described herein. Preferably, the compound of the invention is present in the formulation in a therapeutically effective amount, *e.g.*, an amount effective to treat a sphingosine 1-phosphate associated disorder.

Such pharmaceutically acceptable formulations typically include one or more compounds of the invention as well as one or more pharmaceutically acceptable carriers and/or excipients. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the compounds of the invention, use thereof in the pharmaceutical compositions is contemplated.

Supplementary pharmaceutically active compounds known to treat transplant or autoimmune disease, i.e., immunomodulatory agents and anti-inflammatory agents, as described above, can also be incorporated into the compositions of the invention. Suitable pharmaceutically active compounds that may be used can be found in Harrison's Principles of Internal Medicine (supra).

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.,* intravenous, intradermal, subcutaneous, oral (*e.g.,* inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be

enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injection include sterile aqueous solutions (where water soluble) or dispersions, or sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor El™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the pharmaceutical composition must be sterile and should be fluid to the extent that easy syringability exists. It must also be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the compound of the invention in the required amount in an appropriate solvent with one or a combination of the ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the compound plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compound of the invention can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also include an enteric coating. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible

binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds of the invention are delivered in the form of an aerosol spray from a pressured container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the compounds of the invention are formulated into ointments, salves, gels, or creams as generally known in the art.

The present pharmaceutical compositions can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be:used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811, U.S. Pat. No. 5,455,044 and U.S. Pat. No. 5,576,018, and U.S. Pat. No. 4,883,666, the contents of all of which are incorporated herein by reference.

The compounds of the invention can also be incorporated into pharmaceutical compositions which allow for the sustained delivery of the compounds to a subject for a period of at least several weeks to a month or more. Such formulations are described in published PCT application no. WO 02/74247, incorporated herein by reference.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of a compound of the invention calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the unit dosage forms of the invention are dictated by and directly dependent on the unique characteristics of the compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such compounds for the treatment of individuals.

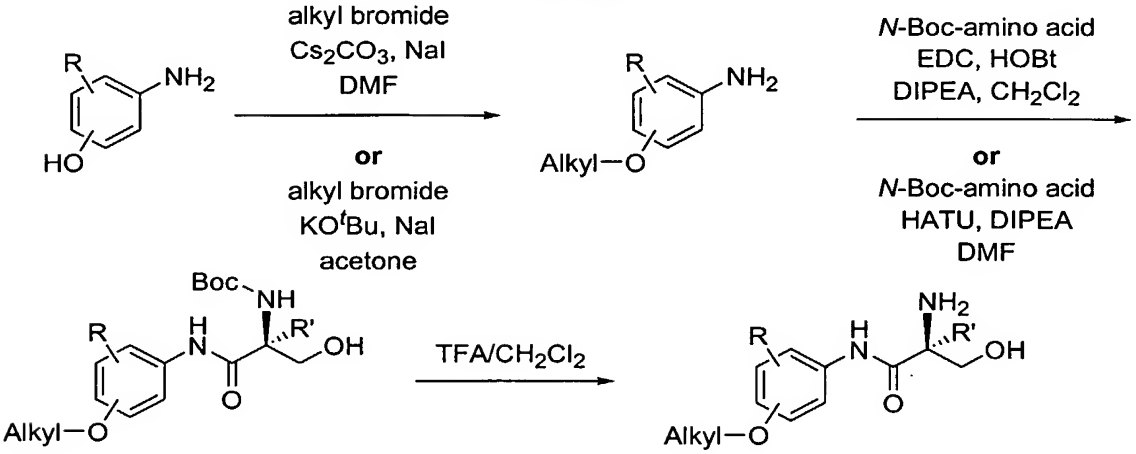
This invention is further illustrated by the following examples, which should not be construed as limiting. The contents of all references, patents, patent applications cited throughout this application are incorporated herein by reference.

EXAMPLES

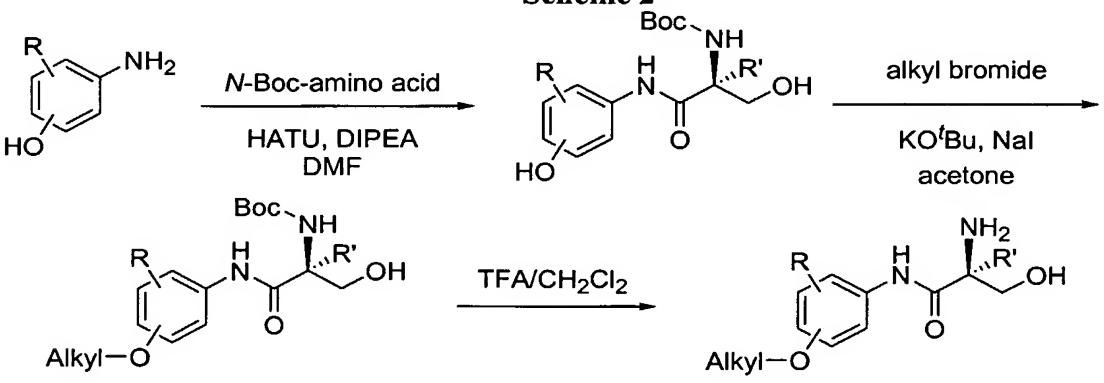
Example 1: Synthesis of Phenylamide Compounds with Alkoxy Tail Group

Certain of the target compounds were synthesized using either the method illustrated in Scheme 1 or the method illustrated in Scheme 2. In Scheme 1, alkylation of the hydroxyl group of a substituted aminophenol is achieved using alkyl bromide and a catalytic amount of NaI in the presence of either Cs_2CO_3 in DMF (60 °C) or KO^{t}Bu in acetone (50 °C). The amino group of the desired intermediate is then acylated with Boc-protected amino acid using either N-ethylcarbodiimide (EDC), 1-hydroxybenzotriazole (HOBt), and N,N-diisopropylethylamine (DIPEA) in CH_2Cl_2 or *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) and DIPEA in DMF. The final compound was obtained in good yields from Boc deprotection of the later intermediate with 30% trifluoroacetic acid (TFA) in CH_2Cl_2. Scheme 2 provides an alternative approach to synthesis of the desired final compound in which the amino group of the aminophenol is acylated first, followed by alkylation of the hydroxyl residue.

Scheme 1



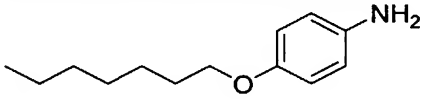
Scheme 2



Alkylation of hydroxyl group

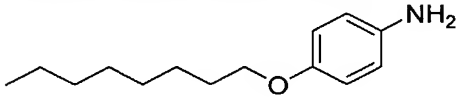
To a solution of desired substituted aminophenol (0.50 g, 1.0 equiv) and NaI (0.1 equiv) in acetone (10 mL) was added a 1.0 M solution of KO^{t}Bu in tetrahydrofuran (THF) (1.1 equiv, 2.1 equiv was used if aminophenol was a hydrochloride salt). To the reaction mixture was added the desired alkyl bromide (1.1 equiv). The reaction was stirred and heated under an atmosphere of nitrogen at 50 °C for 12-24 hours. The reaction was then diluted with EtOAc (25 mL) and washed with H_2O (2 x 25 mL) and saturated NaCl (1 x 25 mL). The organic layer was dried over anhydrous $MgSO_4$ then the solvent removed *in vacuo*. The crude produce was purified using silica gel column chromatography (3:1 Hex:EtOAc).

4-(Heptyloxy)benzenamine:



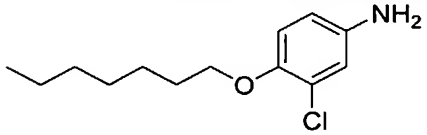
The product was obtained as a yellowish-brown solid in 71% (0.47 g) yield. TLC (3:1 Hex:EtOAc), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69-6.74 (m, 2H), 6.59-6.63 (m, 2H), 3.86 (t, 2H, J = 6.8 Hz), 3.40 (br s, 2H), 1.68-1.78 (m, 2H), 1.21-1.48 (m, 8H), 0.88 (t, 3H, J = 6.8 Hz).

4-(Octyloxy)benzenamine:



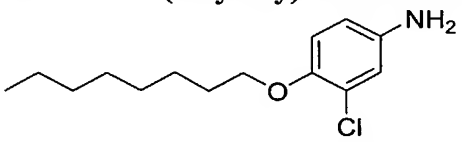
The product was obtained as brownish thick oil in 59% (0.45 g) yield. TLC (3:1 Hex:EtOAc), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69-6.74 (m, 2H), 6.59-6.63 (m, 2H), 3.86 (t, 2H, J = 6.9 Hz), 3.41 (br s, 2H), 1.69-1.79 (m, 2H), 1.22-1.47 (m, 10H), 0.88 (t, 3H, J = 7.1 Hz).

3-Chloro-4-(heptyloxy)benzenamine:



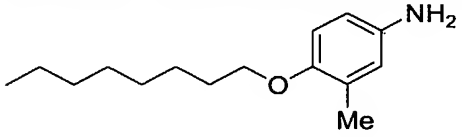
The product was obtained as a white solid in 51% (0.43 g) yield. TLC (3:1 Hex:EtOAc), R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, 1H, J = 8.5 Hz), 6.72 (d, 1H, J = 2.8 Hz), 6.50 (dd, 1H, J = 8.5 Hz, J = 2.8 Hz), 3.91 (t, 2H, J = 6.8 Hz), 3.44 (br s, 2H), 1.73-1.82 (m, 2H), 1.24-1.52 (m, 8H), 0.89 (t, 3H, J = 6.8 Hz).

3-Chloro-4-(octyloxy)benzenamine:



The product was obtained as a white solid in 65% (0.58 g) yield. TLC (3:1 Hex:EtOAc), R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, 1H, J = 8.4 Hz), 6.72 (d, 1H, J = 2.8 Hz), 6.51 (dd, 1H, J = 8.4 Hz, J = 2.8 Hz), 3.91 (t, 2H, J = 6.4 Hz), 3.44 (br s, 2H), 1.73-1.81 (m, 2H), 1.23-1.51 (m, 10H), 0.88 (t, 3H, J = 7.1 Hz).

3-Methyl-4-(octyloxy)benzenamine:

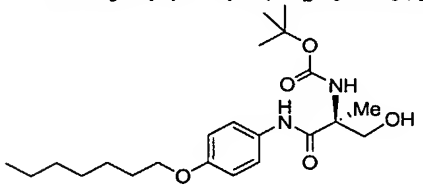


The product was obtained as a yellowish oil in 85% (0.81 g) yield. TLC (3:1 Hex:EtOAc), R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (d, 1H, J = 8.4 Hz), 6.51 (d, 1H, J = 2.4 Hz), 6.45 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz), 3.85 (t, 2H, J = 6.8 Hz), 3.40 (br s, 2H), 2.15 (s, 3H), 1.73-1.80 (m, 2H), 1.23-1.50 (m, 10H), 0.90 (t, 3H, J = 6.8 Hz).

Acylation of substituted alkoxy-benzenamines:

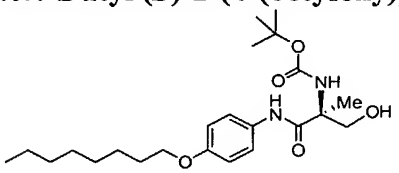
To a solution of the desired substituted alkoxy-benzenamines (0.20 g, 1.0 equiv) and *N*-protected amino acid (1.0 equiv) in DMF (10 mL) was added DIPEA (3.0 equiv) and HATU (1.2 equiv). The reaction mixture was stirred at room temperature under an atmosphere of nitrogen 12-24 hours. The reaction was then diluted with EtOAc (25 mL) and washed with 10% NH_4Cl (2 x 25 mL), 5% $NaHCO_3$ (2 x 25 mL), and saturated NaCl (1 x 25 mL). The organic layer was dried over anhydrous $MgSO_4$ then the solvent removed *in vacuo*. The crude produce was purified using silica gel column chromatography.

***tert*-Butyl (*S*)-2-(4-(heptyloxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate:**



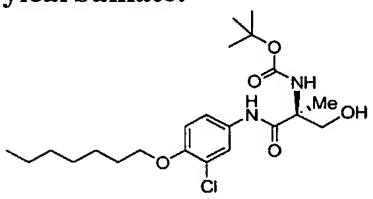
The product was obtained as a brownish solid in 78% (0.29 g) yield. TLC (1:1 EtOAc:Hex), R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (br s, 1H), 7.37 (d, 2H, J = 8.8 Hz), 6.83 (d, 2H, J = 8.8), 5.57 (br s, 1H), 4.02-4.12 (m, 1H), 3.91 (t, 2H, J = 6.4 Hz), 3.55 (br t, 1H), 3.27 (br t, 1H), 1.71-1.80 (m, 2H), 1.55 (s, 3H), 1.46 (s, 9H), 1.23-1.50 (m, 8H), 0.89 (t, 3H, J = 7.2 Hz).

***tert*-Butyl (*S*)-2-(4-(octyloxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate:**



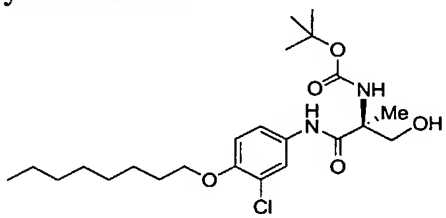
The product was obtained as a brownish solid in 49% (0.185 g) yield. TLC (1:1 EtOAc:Hex), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (br s, 1H), 7.36 (d, 2H, J = 9.0 Hz), 6.83 (d, 2H, J = 9.0), 5.59 (br s, 1H), 4.03-4.13 (m, 1H), 3.91 (t, 2H, J = 6.4 Hz), 3.55 (br t, 1H), 3.26 (br t, 1H), 1.71-1.80 (m, 2H), 1.56 (s, 3H), 1.46 (s, 9H), 1.23-1.50 (m, 10H), 0.88 (t, 3H, J = 6.8 Hz).

***tert*-Butyl (*S*)-2-(3-chloro-4-(heptyloxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate:**



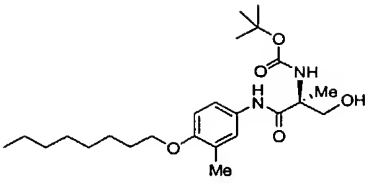
The product was obtained as an off white solid in 47% (0.169 g) yield. TLC (1:1 EtOAc:Hex), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (br s, 1H), 7.53 (d, 1H, J = 2.4 Hz), 7.28 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 6.84 (d, 1H, J = 8.8), 5.75 (br s, 1H), 4.02-4.10 (m, 1H), 3.98 (t, 2H, J = 6.4 Hz), 3.54 (br t, 1H), 3.21 (br t, 1H), 1.76-1.85 (m, 2H), 1.55 (s, 3H), 1.46 (s, 9H), 1.24-1.51 (m, 8H), 0.89 (t, 3H, J = 7.2 Hz).

***tert*-Butyl (*S*)-2-(3-chloro-4-(octyloxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate:**



The product was obtained as a brownish solid in 40% (0.158 g) yield. TLC (1:1 EtOAc:Hex), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (br s, 1H), 7.57 (d, 1H, J = 2.4 Hz), 7.28 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 6.84 (d, 1H, J = 8.8), 5.58 (br s, 1H), 4.02-4.11 (m, 1H), 3.98 (t, 2H, J = 6.4 Hz), 3.54 (br t, 1H), 3.21 (br t, 1H), 1.76-1.85 (m, 2H), 1.53 (s, 3H), 1.47 (s, 9H), 1.23-1.53 (m, 10H), 0.88 (t, 3H, J = 6.8 Hz).

***tert*-Butyl (*S*)-2-(3-methyl-4-(octyloxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate:**

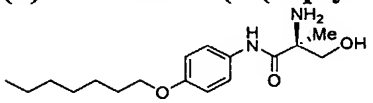


The product was obtained as an off white solid in 93% (0.133 g) yield. TLC (1:3 EtOAc:Hex), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.26 (m, 2H), 6.70 (d, 1H, *J* = 8.0 Hz), 5.74 (br s, 1H), 3.94-4.08 (m, 1H), 3.89 (t, 2H, *J* = 6.4 Hz), 3.71-3.79 (br t, 1H), 3.55-3.67 (br t, 1H), 2.19 (s, 3H), 1.72-1.82 (m, 2H), 1.55 (s, 3H), 1.45 (s, 9H), 1.22-1.52 (m, 10H), 0.89 (t, 3H, *J* = 6.8 Hz).

Removal of Boc protecting group:

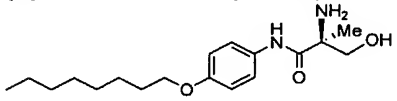
To a solution of the desired starting material (65 mg) in dry CH_2Cl_2 (2 mL) was added trifluoroacetic acid (TFA, 1 mL). The reaction mixture was stirred at room temperature 3-4 hours then evaporated to dryness under reduced pressure. The obtained residue was then azeotroped with CH_2Cl_2 (2 x 2 mL) to remove any excess TFA. The final product was either used as is or purified by reverse phase prep HPLC.

(*S*)-2-Amino-*N*-(4-(heptyloxy)phenyl)-3-hydroxy-2-methylpropanamide:



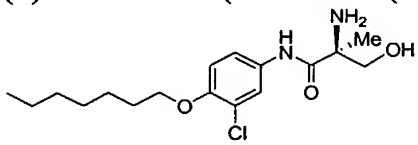
The product was obtained as a white solid in 73% (30 mg) yield. MS (ESI, M+H$^+$) = 309.47

(*S*)-2-Amino-3-hydroxy-2-methyl-*N*-(4-(octyloxy)phenyl)propanamide:



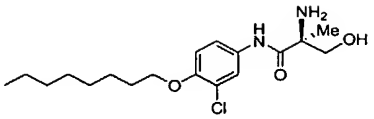
The product was obtained as a white solid in 78% (40 mg) yield. MS (ESI, M+H$^+$) = 323.65

(*S*)-2-Amino-*N*-(3-chloro-4-(heptyloxy)phenyl)-3-hydroxy-2-methylpropanamide:



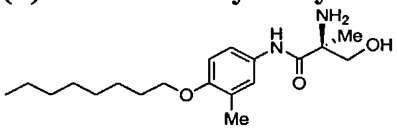
The product was obtained as a white solid in 24% (40 mg) yield. MS (ESI, M+H$^+$) = 343.39

(*S*)-2-Amino-*N*-(3-chloro-4-(octyloxy)phenyl)-3-hydroxy-2-methylpropanamide:



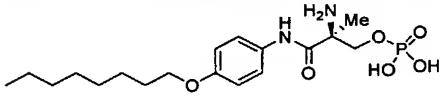
The product was obtained as a white solid in 81% (25 mg) yield. MS (ESI, M+H$^+$) = 357.98

(*S*)-2-Amino-3-hydroxy-2-methyl-*N*-(3-methyl-4-(octyloxy)phenyl)propanamide:



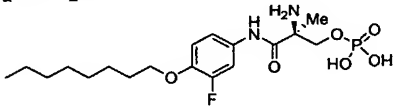
The product was obtained as a white solid in 32% (40 mg) yield. MS (ESI, M+H$^+$) = 337.56.

(*S*)-2-(4-(Octyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate



The product was obtained as white solid in 63% (24.9 mg) yield. MS (ESI, M+H$^+$) = 403.71; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.04 (s, 1H), 7.50 (d, 2H, J = 8.8 Hz), 6.87 (d, 2H, J = 8.8 Hz), 4.25 (dd, 1H, J = 12.4 Hz, J = 6.8 Hz), 4.10 (dd, 1H, J = 12.8 Hz, J = 6.8 Hz), 3.90 (t, 2H, J = 6.4 Hz), 1.62-1.72 (m, 2H), 1.47 (s, 3H), 1.20-1.44 (m, 10H), 0.85 (t, 3H, J = 7.2 Hz).

(*S*)-2-(3-Fluoro-4-(octyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate



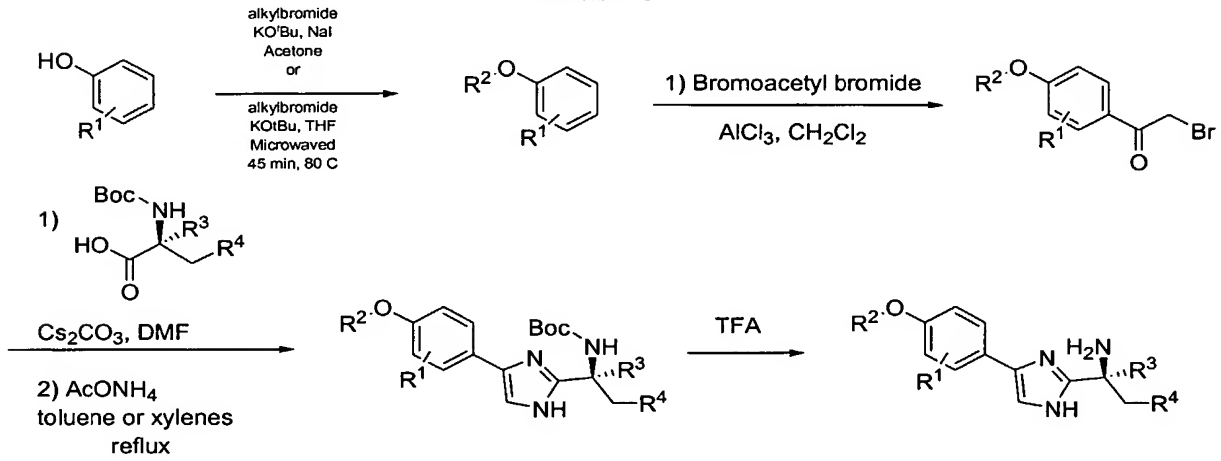
The product was obtained as white solid in 42% (2.5 mg) yield. MS (ESI, M+H$^+$) = 421.17; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.19 (s, 1H), 7.52 (dd, 1H, J = 14.0 Hz, J = 2.4 Hz), 7.27 (dd, 1H, J = 10.0Hz, J = 1.2 Hz), 7.05 (t, 1H, J = 9.6Hz), 4.20 (dd, 1H, J = 11.6 Hz, J = 6.4 Hz), 4.03 (dd, 1H, J = 11.6 Hz, J = 6.8 Hz), 3.93 (t, 2H, J = 6.4 Hz), 1.59-1.68 (m, 2H), 1.41 (s, 3H), 1.14-1.38 (m, 10H), 0.80 (t, 3H, J = 7.2 Hz).

Example 2: Synthesis of Phenylimidazole Compounds with Alkoxy Tail Group

The desired compounds were synthesized as described in Scheme 3. Substituted phenols were alkylated with the appropriate alkyl bromide using KO^{t}Bu in acetone and a catalytic amount of NaI at 50 °C, or in a microwave at 80 °C using KO^{t}Bu in THF.

Friedel-Crafts acylation of the corresponding phenyl ether provides the desired bromoacetophenone precursor. Reaction of the bromoacetophenone with an amino acid gave the amino acid ester as an intermediate which, upon intramolecular cyclization in the presence of excess ammonium acetate, provided the desired phenylimidazole. The phenylimidazole was either deprotected to remove the Boc group using 30% TFA in CH_2Cl_2, or was phosphorylated as illustrated in Scheme 4.

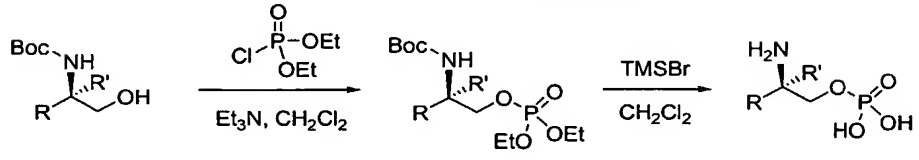
Scheme 3



General method for phosphate synthesis

This method is illustrated in Scheme 4 below. To a solution of the Boc-protected aminoalcohol (1.0 equiv) in dry CH_2Cl_2 at room temperature was added excess diethyl chlorophosphate (10-20 equiv) and triethylamine (2.5 equiv) and the reaction stirred for 12-18 hours. The crude was then loaded onto a silica gel column chromatography, as is, to purify the desired phospho-diester. The phopho-diester intermediate was reacted with excess bromotrimethylsilane (20 equiv) in dry CH_2Cl_2 at room temperature, under an atmosphere of nitrogen, over a period of 6-10 hours afforded the final phosphate which was purified by reverse-phase preparative HPLC.

Scheme 4



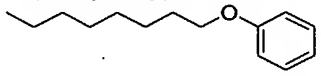
General methods for alkylation of substituted phenols

Procedure A: To a solution of desired substituted phenol (0.50 g, 1.0 equiv) and NaI (0.1 equiv) in acetone (10 mL) was added a 1.0 M solution of KO'Bu in THF (1.1 equiv). To the reaction mixture is then added the desired alkyl bromide (1.1 equiv). The reaction was stirred and heated under an atmosphere of nitrogen at 50 °C for 12-24 hours. The

reaction was then diluted with EtOAc (25 mL) and washed with H_2O (2 x 25 mL) and saturated NaCl (1 x 25 mL). The organic layer was dried over anhydrous $MgSO_4$ then the solvent removed *in vacuo*. The crude product was purified using silica gel column chromatography (9:1 Hex:EtOAc).

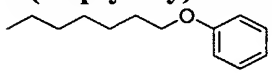
Procedure B: To a microwave tube containing the substituted phenol (0.50 g, 1.0 equiv) was added a 1.0 M solution of KO^{t}Bu in THF (1.1 equiv). To the reaction mixture was added the desired alkyl bromide (1.1 equiv). The reaction mixture was then microwaved at 80 °C for 45 minutes. The reaction was then diluted with EtOAc (25 mL) and washed with H_2O (2 x 25 mL) and saturated NaCl (1 x 25 mL). The organic layer was dried over anhydrous $MgSO_4$ then the solvent removed *in vacuo*. The crude product was purified using silica gel column chromatography (9:1 Hex:EtOAc).

1-(Octyloxy)benzene



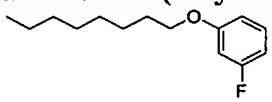
The product was obtained as an off white solid in 79% (1.0 g) yield. TLC (1:3 EtOAc:Hex), R_f = 0.85; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 2H), 6.89 (m, 3H), 3.93 (t, 2H, J = 6.4 Hz), 1.76-1.81 (m, 2H), 1.42-1.48 (m, 2H), 1.20-1.38 (m, 8H), 0.89 (t, 3H, J = 6.8 Hz).

1-(Heptyloxy)benzene



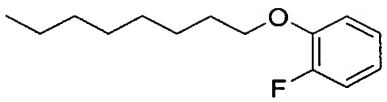
The product was obtained as brownish thick oil in 59% (0.45 g) yield. TLC (1:3 EtOAc:Hex), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69-6.74 (m, 2H), 6.59-6.63 (m, 2H), 3.86 (t, 2H, J = 6.9 Hz), 3.41 (br s, 2H), 1.69-1.79 (m, 2H), 1.22-1.47 (m, 10H), 0.88 (t, 3H, J = 7.1 Hz).

1-Fluoro-3-(octyloxy)benzene



The product was obtained as a colorless oil in 84% (2.10 g) yield. TLC (1:9 EtOAc:Hex), R_f = 0.8; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.23 (m, 1H), 6.57-6.69 (m, 3H), 3.93 (t, 2H, J = 6.4 Hz), 1.73-1.82 (m, 2H), 1.23-1.50 (m, 10H), 0.89 (t, 3H, J = 7.2 Hz).

1-Fluoro-2-(octyloxy)benzene

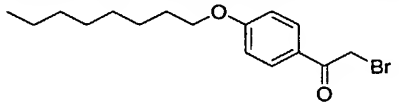


The product was obtained as a yellowish solid in 71% (0.92 g) yield. TLC (1:3 EtOAc:Hex), R_f = 0.83; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08-7.10 (m, 2H), 6.94 (dd, 1H), 6.80-6.88 (m, 1H), 4.02 (t, 2H, J = 6.8 Hz), 1.76-1.82 (m, 2H), 1.42-1.48 (m, 2H), 1.20-1.38 (m, 8H), 0.88 (t, 3H, J = 6.8 Hz).

General method for Friedel-Crafts acylation

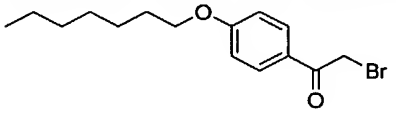
To a solution of the desired phenyl ether (8.92 mmol, 1.0 equiv) in dry CH_2Cl_2 (20 mL) at -20 °C (water/salt bath) is added $AlCl_3$ (1.1 equiv) in portions. Bromoacetyl bromide (1.2 equiv) is then added dropwise to the reaction mixture over a period of 10-15 min. The reaction was then allowed to warm up to 0 °C or room temperature and monitored by TLC (reaction time generally 4-12 hours). The mixture was diluted with CH_2Cl_2 (50 mL), washed with H_2O (2 x 50 mL), and saturated NaCl (1 x 50 mL). The organic layer was dried over anhydrous $MgSO_4$ then the solvent was removed *in vacuo*. The crude product was purified using silica gel column chromatography (9:1 Hex:EtOAc).

2-Bromo-1-(4-(octyloxy)phenyl)ethanone



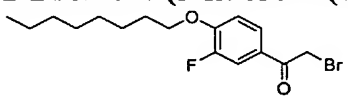
The product was obtained as an off white solid in 59% (0.461 g) yield. TLC (1:3 EtOAc:Hex), R_f = 0.85; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, 2H, J = 6.0 Hz), 7.22 (d, 2H, J = 8.0 Hz), 4.68 (s, 2H), 4.31 (t, 2H, J = 6.8 Hz), 2.09 (m, 2H), 1.75 (m, 2H), 1.58 (m, 10H), 1.17 (t, 3H, J = 6.8 Hz).

2-Bromo-1-(4-(heptyloxy)phenyl)ethanone



The product was obtained as an off white solid in 30% (0.93 g) yield. TLC (1:3 EtOAc:Hex), R_f = 0.68; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, 2H, J = 7.2 Hz), 6.94 (d, 2H, J = 8.8 Hz), 4.39 (s, 2H), 4.03 (t, 2H, J = 6.8 Hz), 1.82 (m, 2H), 1.45 (m, 2H), 1.31 (m, 6H), 0.90 (t, 3H, J = 7.2 Hz).

2-Bromo-1-(3-fluoro-4-(octyloxy)phenyl)ethanone



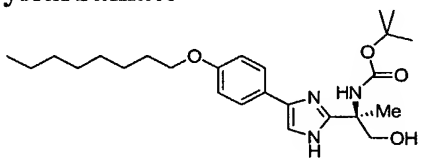
The product was obtained as a whitish solid in 39% (0.1 g). TLC (1:3 EtOAc:Hex), R_f = 0.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.76 (m, 2H), 7.00 (t, 1H, J = 8.0 Hz), 4.37 (s, 2H), 4.11 (t, 2H, J = 6.4 Hz), 1.82-1.88 (m, 2H), 1.44-1.53 (m, 2H), 1.28-1.34 (m, 8H), 0.88 (t, 3H, J = 6.8 Hz).

General method for imidazole synthesis

A mixture of desired amino acid (1.0 equiv) and Cs_2CO_3 (0.5 equiv) was stirred in DMF (4 mL) for 5 minutes then to the solution was added the desired bromo-ketone (0.77 mmol, 1.0 equiv) then the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with EtOAc (25 mL) and washed with H_2O (2 x 25 mL), and saturated NaCl (1 x 25 mL) to remove access DMF and CsBr salt. The organic layer was dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo* (the DMF could also be removed either under reduced pressure without the necessity for the work-up).

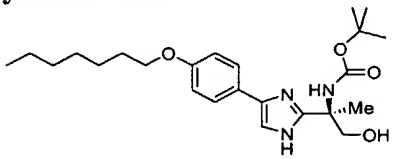
To the obtained ester was then added excess (~20 eq) ammonium acetate, and the mixture was suspended in either toluene or xylenes and refluxed for 4-6 hours under Dean-Stark conditions. The mixture was diluted with EtOAc (25 mL) and washed with H_2O (2 x 25 mL), and saturated NaCl (1 x 25 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified using silica gel column chromatography.

tert-Butyl-(R)-1-hydroxy-2-(4-(4-(octyloxy)phenyl)-1H-imidazol-2-yl)propan-2-ylcarbamate



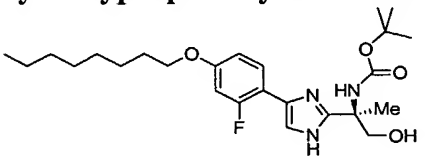
The product was obtained as a colorless foam in 35% (72 mg) yield. TLC (1:1 EtOAc:Hex), R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (br s, 1H), 7.63 (d, 2H, J = 8.4 Hz), 7.10 (br s, 1H), 6.90 (d, 2H, J = 8.4), 5.66 (br s, 1H), 4.85 (br s, 1H), 4.31 (d, 1H, J = 11.2), 3.96 (t, 2H, J = 6.8 Hz), 3.62 (d, 1H, J = 11.2 Hz), 1.73-1.82 (m, 2H), 1.66 (s, 3H), 1.44 (s, 9H), 1.24-1.52 (m, 10H), 0.89 (t, 3H, J = 7.2 Hz).

***tert*-Butyl-(*R*)-2-(4-(4-(heptyloxy)phenyl)-1*H*-imidazol-2-yl)-1-hydroxypropan-2-ylcarbamate**



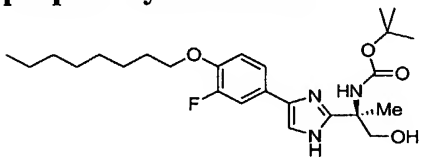
The product was obtained as a brownish solid in 17% (56 mg) yield. TLC (2:1 EtOAc:Hex), R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 2H, J = 8.4 Hz), 7.09 (br s, 1H), 6.90 (d, 2H, J = 8.4), 5.70 (br s, 1H), 4.30 (d, 1H, J = 11.2), 3.97 (t, 2H, J = 6.8 Hz), 3.63 (d, 1H, J = 11.2 Hz), 1.74-1.83 (m, 2H), 1.66 (s, 3H), 1.43 (s, 9H), 1.24-1.50 (m, 8H), 0.90 (t, 3H, J = 7.2 Hz).

***tert*-Butyl-(*R*)-2-(4-(2-fluoro-4-(octyloxy)phenyl)-1*H*-imidazol-2-yl)-1-hydroxypropan-2-ylcarbamate**



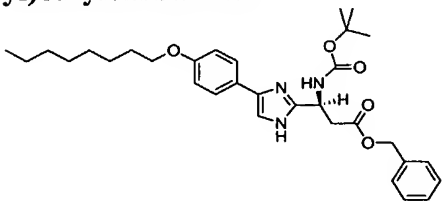
The product was obtained as a yellowish-brown solid in 20% (320 mg) yield. TLC (1:2 EtOAc:Hex), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.25 (br s, 1H), 6.73 (dd, 1H, J = 12.9 Hz, J = 2.4 Hz), 6.66 (dd, 1H, J = 12.9 Hz, J = 2.4 Hz), 5.68 (br s, 1H), 4.31 (d, 1H, J = 11.2), 3.95 (t, 2H, J = 6.4 Hz), 3.63 (d, 1H, J = 11.2 Hz), 1.74-1.83 (m, 2H), 1.67 (s, 3H), 1.44 (s, 9H), 1.22-1.52 (m, 10H), 0.89 (t, 3H, J = 7.0 Hz).

***tert*-Butyl (*R*)-2-(4-(3-fluoro-4-(octyloxy)phenyl)-1H-imidazol-2-yl)-1-hydroxy propan-2-ylcarbamate**



The final product was obtained as a white solid in 31% (30 mg). TLC (1:3 EtOAc:Hex), R_f = 0.16; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.4 (m, 2H), δ 7.101 (s, 1H), 6.944 (t, 1H, J = 8.4 Hz), 4.3 (d, 1H, J = 11.6), 4.033 (t, 2H, J = 6.8), 3.62 (d, 1H, J = 11.6 Hz), 1.81-1.86 (m, 2H), 1.66 (s, 3H), 1.44-1.52 (m, 10H), 0.88 (t, 3H, J = 6.8 Hz). MS (ESI, M+H$^+$) = 364.5

***tert*-Butyl (S)-2-((benzyloxy)carbonyl)-1-(4-(4-(octyloxy)phenyl)-1*H*-imidazol-2-yl)ethylcarbamate**

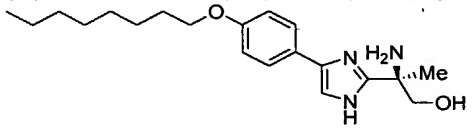


The product was obtained as a colorless oil in 64% (160 mg) yield. TLC (2:1 EtOAc:Hex), R_f = 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (br s, 1H), 7.28-7.35 (m, 7H), 7.08 (s, 1H), 6.89 (d, 2H, J = 9.2 Hz), 5.90 (br s, 1H), 5.08-5.21 (m, 3H), 3.97 (t, 2H, J = 6.0 Hz), 3.26 (br m, 1H), 3.00 (dd, 1H, J = 16.4 Hz, J = 7.2 Hz), 1.74-1.84 (m, 2H), 1.46 (s, 9H), 1.23-1.54 (m, 10H), 0.89 (t, 3H, J = 7.2 Hz).

General method for removal of Boc protecting group

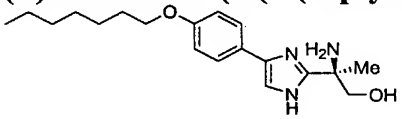
To a solution of the desired starting material (100 mg) in CH_2Cl_2 (2 mL) was added TFA (1 mL). The reaction mixture was stirred at room temperature 2 hours then evaporated to dryness under reduced pressure. The final product was purified by reverse phase preparative HPLC.

(*R*)-2-Amino-2-(4-(4-(octyloxy)phenyl)-1*H*-imidazol-2-yl)propan-1-ol



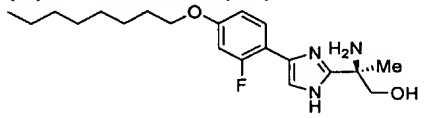
The product was obtained as a white solid in 81% (29 mg) yield. MS (ESI, M+H$^+$) = 346.30; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (br s, 2H), 7.67 (d, 2H, J = 8.4 Hz), 7.50 (br s, 1H), 6.92 (d, 2H, J = 8.4), 5.82 (br s, 1H), 3.94 (t, 2H, J = 6.4 Hz), 3.75 (d, 1H, J = 11.6 Hz), 3.64 (d, 1H, J = 11.6 Hz), 1.65-1.74 (m, 2H), 1.55 (s, 3H), 1.22-1.45 (m, 10H), 0.85 (t, 3H, J = 7.2 Hz).

(*R*)-2-Amino-2-(4-(4-(heptyloxy)phenyl)-1*H*-imidazol-2-yl)propan-1-ol



The product was obtained as a white solid in 99% (58 mg) yield. MS (ESI, M+H$^+$) = 332.60; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (br s, 2H), 7.67 (d, 2H, J = 8.4 Hz), 7.40 (br s, 1H), 6.92 (d, 2H, J = 8.4), 5.66 (br s, 1H), 3.94 (t, 2H, J = 6.8 Hz), 3.74 (d, 1H, J = 11.6 Hz), 3.64 (d, 1H, J = 11.6 Hz), 1.64-1.76 (m, 2H), 1.55 (s, 3H), 1.22-1.44 (m, 8H), 0.86 (t, 3H, J = 7.0 Hz).

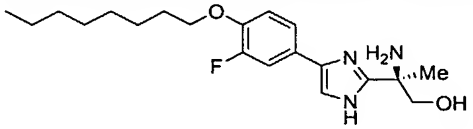
(*R*)-2-Amino-2-(4-(2-fluoro-4-(octyloxy)phenyl)-1*H*-imidazol-2-yl)propan-1-ol



The product was obtained as a white solid in 75% (77 mg) yield. MS (ESI, M+H$^+$) = 364.60; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (br s, 2H), 7.93 (br t, 1H), 7.38 (d, 2H, J = 3.6 Hz), 6.81-6.70 (m, 2H), 5.67 (br s, 1H), 3.97 (t, 2H, J = 6.2 Hz), 3.74 (d,

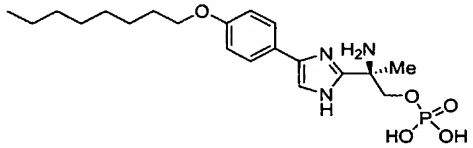
1H, J = 11.6 Hz), 3.66 (d, 1H, J = 11.6 Hz), 1.64-1.75 (m, 2H), 1.55 (s, 3H), 1.21-1.44 (m, 10H), 0.85 (t, 3H, J = 7.2 Hz).

(*R*)-2-Amino-2-(4-(3-fluoro-4-(octyloxy)phenyl)-1*H*-imidazol-2-yl)propan-1-ol



The final product was obtained as a white solid in 31% (30 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.4 (m, 2H), δ 7.101 (s, 1H), 6.944 (t, 1H, J = 8.4 Hz), 4.3 (d, 1H, J = 11.6), 4.033 (t, 2H, J = 6.8), 3.62 (d, 1H, J = 11.6 Hz), 1.81-1.86 (m, 2H), 1.66 (s, 3H), 1.52-1.44 (m, 10H), 0.88 (t, 3H, J = 6.8 Hz). MS (ESI, M+H$^+$) = 364.5

(*R*)-2-Amino-2-(4-(4-(octyloxy)phenyl)-1*H*-imidazol-2-yl)propyl dihydrogen phosphate

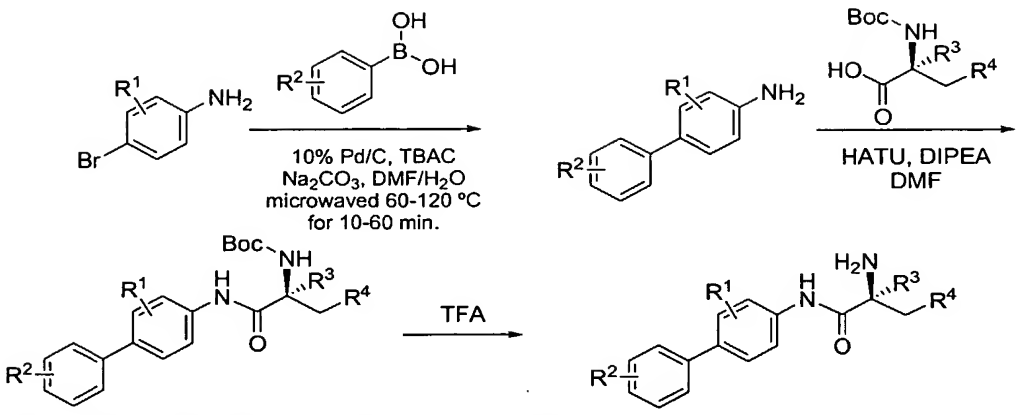


The product was obtained as white solid in 69% (22.8 mg) yield. MS (ESI, M+H$^+$) = 426.65; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (d, 2H, J = 8.6 Hz), 7.48 (s, 1H), 6.91 (d, 2H, J = 8.6 Hz), 4.16 (dd, 1H, J = 10.8 Hz, J = 6.8 Hz), 4.05 (dd, 1H, J = 10.8 Hz, J = 6.8 Hz), 3.94 (t, 2H, J = 6.8 Hz), 1.64-1.73 (m, 2H), 1.59 (s, 3H), 1.21-1.45 (m, 10H), 0.85 (t, 3H, J = 7.2 Hz).

Example 3: Synthesis of Phenylamide Compounds with Aryl Tail Groups

Several biphenyls were synthesized using the process described in Scheme 5. Microwave assisted Suzuki cross-coupling of substituted arylboronic acids with substituted anilines afforded good to excellent yields of the biaryl amine intermediates. Furthermore, the acylation of the substituted biaryl amines with desired headpiece followed by deprotection of the Boc group afforded the final compounds.

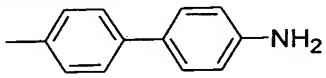
Scheme 5



General method for Suzuki cross-coupling

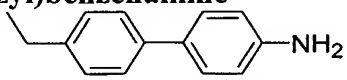
To a mixture of a substituted bromoaniline (1.0 equiv), substituted aryl boronic acid (1.2 equiv), 10% Pd on carbon (0.1 equiv), tetrabutylammonium chloride (0.1 equiv), and sodium carbonate (1.0 to 2.0 equiv), in a microwave tube was added a 1:1 mixture of DMF:H_2O. The mixture was then heated to 60-120 °C for 10-60 minutes using a microwave. The reaction is then diluted with EtOAc (25 mL) and washed with H_2O (2 x 25 mL) and saturated NaCl (1 x 25 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent removed in vacuo. The crude product was purified using silica gel column chromatography (Hex:EtOAc) as required.

4-(4-tolyl)benzenamine



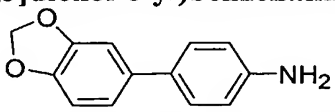
The product was obtained as a white solid in 66% (140 mg) yield. TLC (2:1 Hex:EtOAc), R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.38 (m, 4H), 7.12 (d, 2H, J = 8.4 Hz), 6.67 (d, 2H, J = 8.4 Hz), 3.60 (br s, 2H), 2.31 (s, 3H).

4-(4-ethylbenzyl)benzenamine



The product was obtained as a white solid in 87% (200 mg) yield. TLC (2:1 Hex:EtOAc), R_f = 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.48 (m, 4H), 7.24 (d, 2H, J = 8.0 Hz), 6.75 (d, 2H, J = 8.0 Hz), 3.40 (br s, 2H), 2.68 (q, 2H, J = 7.2 Hz), 1.27 (t, 3H, J = 7.2 Hz).

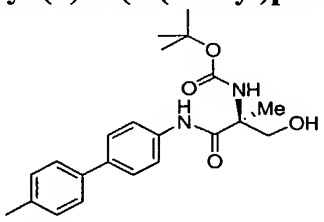
4-(benzo[*d*][1,3]dioxol-6-yl)benzenamine



The product was obtained as a white solid in 75% (186 mg) yield. TLC (2:1 Hex:EtOAc), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.58 (m, 2H), 7.44-7.49 (m,

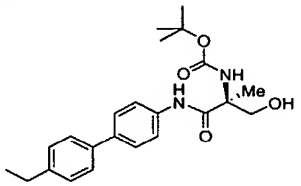
2H), 7.01-7.06 (m, 2H), 6.86 (dd, 1H, J = 7.6 Hz, J = 1.4 Hz), 6.00 (s, 2H), 3.40 (br s, 2H).

***tert*-butyl (*S*)-2-(4-(4-tolyl)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate**



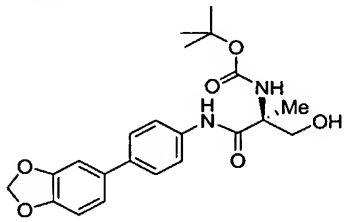
The product was obtained as a white solid in 35% (104 mg) yield. TLC (1:1 Hex:EtOAc), R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.43-7.53 (m, 4H), 7.36-7.42 (m, 2H), 7.15-7.25 (m, 2H), 5.56 (br s, 1H), 4.05 (br s, 1H), 3.49 (br s, 1H), 3.13 (br s, 1H), 2.32 (s, 3H), 1.54 (s, 3H), 1.44 (m, 9H).

***tert*-butyl (*S*)-2-(4-(4-ethylbenzyl)phenylcarbamoyl)-1-hydroxypropan-2-yl carbamate**



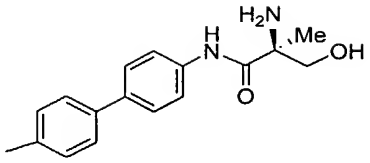
The product was obtained as a white solid in 31% (125 mg) yield. TLC (1:1 Hex:EtOAc), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (br s, 1H), 7.42-7.64 (m, 6H), 7.24-7.32 (m, 2H), 5.62 (br s, 1H), 4.10 (br s, 1H), 3.60 (br s, 1H), 3.20 (br s, 1H), 2.70 (q, 2H, J = 7.0 Hz), 1.55 (s, 3H), 1.45 (m, 9H), 1.30 (t, 3H, J = 7.0 Hz).

***tert*-Butyl (*S*)-2-(4-(benzo[*d*][1,3]dioxol-6-yl)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate**



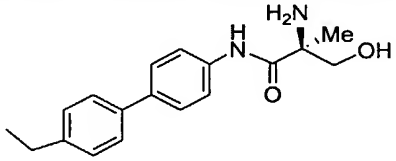
The product was obtained as a white solid in 20% (89 mg) yield. TLC (1:1 Hex:EtOAc), R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.53-7.58 (m, 2H), 7.45-7.50 (m, 2H), 7.01-7.05 (m, 2H), 6.86 (dd, 1H, J = 7.6 Hz, J = 1.2 Hz), 6.00 (s, 2H), 5.62 (br s, 1H), 4.13 (br s, 1H), 3.57 (br s, 1H), 3.20 (br s, 1H), 1.55 (s, 3H), 1.48 (m, 9H).

(*S*)-2-Amino-*N*-(4-(4-tolyl)phenyl)-3-hydroxy-2-methylpropanamide



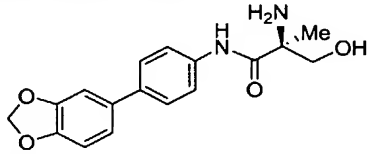
The product was obtained as a white solid in 98% (36 mg) yield. MS (ESI, $M+H^+$) = 285.40; ^1H NMR (400 MHz, DMSO-d_6) δ 9.94 (br s, 1H), 8.16 (br s, 2H), 7.61-7.72 (m, 4H), 7.54 (d, 2H, J = 7.6 Hz), 7.24 (d, 2H, J = 7.6 Hz), 5.78 (t, 1H, J = 4.8 Hz), 4.00 (dd, 1H, J = 11.6 Hz, J = 4.8 Hz), 3.65 (dd, 1H, J = 11.6 Hz, J = 5.2 Hz), 2.32 (s, 3H), 1.50 (s, 3H).

(*S*)-2-Amino-*N*-(4-(4-ethylbenzyl)phenyl)-3-hydroxy-2-methylpropanamide



The product was obtained as a white solid in 64% (28 mg) yield. MS (ESI, $M+H^+$) = 299.30; ^1H NMR (400 MHz, DMSO-d_6) δ 9.95 (br s, 1H), 8.18 (br s, 2H), 7.61-7.72 (m, 4H), 7.55 (d, 2H, J = 8.2 Hz), 7.26 (d, 2H, J = 8.2 Hz), 5.80 (br s, 1H), 4.00 (d, 1H, J = 11.6 Hz), 3.65 (d, 1H, J = 11.6 Hz), 2.61 (q, 2H, J = 7.6 Hz), 1.50 (s, 3H), 1.19 (t, 3H, J = 7.6 Hz).

(*S*)-2-amino-*N*-(4-(benzo[*d*][1,3]dioxol-6-yl)phenyl)-3-hydroxy-2-methylpropanamide



The product was obtained as a white solid in 47% (32 mg) yield. MS (ESI, $M+H^+$) = 315.40; ^1H NMR (400 MHz, DMSO-d_6) δ 9.93 (br s, 1H), 8.17 (br s, 2H), 7.66 (d, 2H, J = 8.4 Hz), 7.59 (d, 2H, J = 8.4 Hz), 7.22 (d, 1H, J = 1.6 Hz), 7.12 (dd, 1H, J = 6.8 Hz, J = 2.0 Hz), 6.97 (d, 1H, J = 8.4 Hz), 6.04 (s, 2H), 5.79 (br s, 1H), 4.00 (d, 1H, J = 11.2 Hz), 3.65 (d, 1H, J = 11.2 Hz), 1.50 (s, 3H).

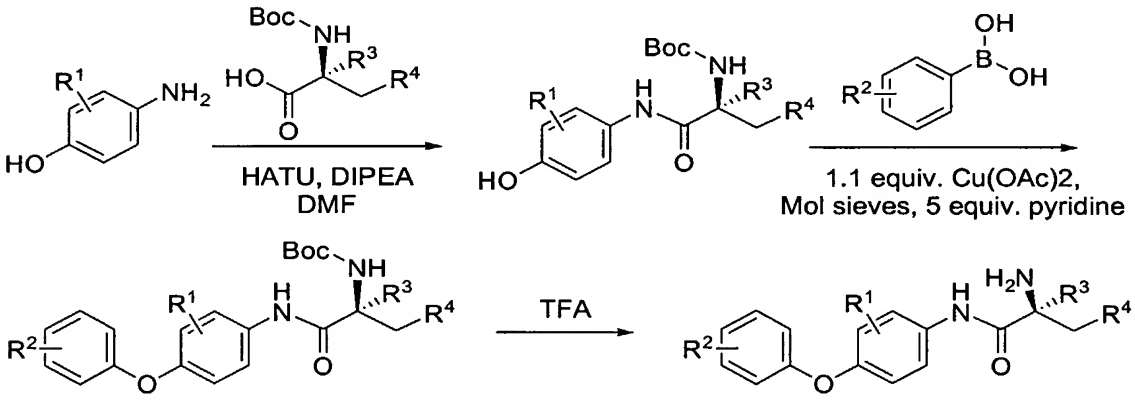
Example 4: Synthesis of Substituted Biaryl Ether Compounds

General method for the synthesis of substituted biaryl ethers

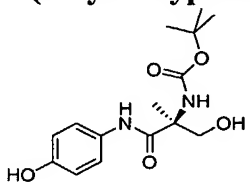
The biaryl ethers were synthesized using the general method shown in Scheme 6. To a flame dried round bottom flask is added the acylated 4-aminophenol (1 equiv. 0.15 gm), cupric acetate [$Cu(OAc)_2$, 1.1. equiv], desired substituted boronic acid (2.5 equiv.), and excess of 4A molecular sieves (0.6 -0.9 gm). Dry dichloromethane (DCM) is then added to the reaction flask followed by the addition of anhydrous pyridine (5.0 equiv.).

Oxygen is then bubbled through the reaction mixture for approximately 2 min and the reaction is stirred over night at room temperature under an atmosphere of oxygen. The following day the reaction mixture was filtered using a plug of celite to remove the molecular sieves, and the filtrate was concentrated to give a greenish solid. The crude product was purified using silica gel chromatography, EtOAc-Hexane gradient, (25% - 100% EtOAc over 30 min.). The fractions corresponding to the product are pooled and the solvent removed *under vacuo* to give product as a white solid.

Scheme 6

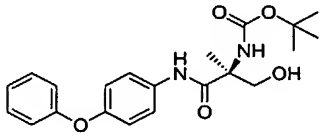


tert-Butyl (S)-2-(4-hydroxyphenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate



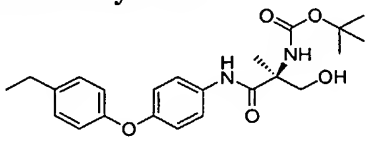
The final product was obtained as a white solid after silica gel purification using an EtOAc-Hexane gradient (15% EtOAc to 80% EtOAc over 25 min.), in 61% yield. TLC (2:1 EtOAc:Hex), R_f (product)= 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), δ 7.34 (d, 2H, J = 8.8 Hz), 6.79 (d, 2H, J = 8.8 Hz), 5.60 (br. s, 1H), 4.06 (m, 1H), 3.58 (d, 1H, J = 12), 1.58 (s, 3H), 1.46 (s, 9H).

(*S*)-[2-Hydroxy-1-methyl-1-(4-phenoxy-phenylcarbamoyl)-ethyl]-carbamic acid *tert*-butyl ester



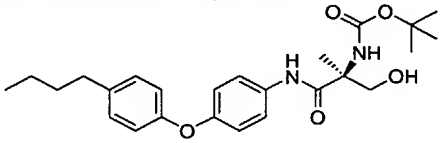
The final product was obtained as white solid following silica gel purification, in 58% yield, (0.08g). TLC (1:1 EtOAc:Hex), R_f = 0.2; MS (ESI, M+H$^+$) = 387.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), δ 7.48 (d, 2H, *J* = 8.8 Hz), 7.30 (m, 2H), 7.07 (m, 1H), 6.97 (m, 4H), 4.16 (s, 1H), 3.65 (s, 1H), 1.58 (s, 3H) 1.46 (s, 9H).

(*S*)-{1-[4-(4-Ethyl-phenoxy)-phenylcarbamoyl]-2-hydroxy-1-methyl-ethyl}-carbamic acid *tert*-butyl ester



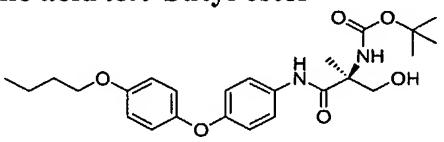
The final product was obtained as white solid following silica gel purification, in 65% yield, (0.05g). TLC (1:1 EtOAc:Hex), R_f = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.6 (s, 1H), δ 7.47 (d, 2H, *J* = 8.0 Hz), 7.13 (d, 2H, *J* = 8.4 Hz), 6.92 (d, 2H, *J* = 10 Hz), 6.88 (m, 2H), 4.05 (m, 1H), 3.64 (d, 1H, J = 10.8), 2.62 (q, 2H, J = 16 Hz, J = 8 Hz), 1.58 (s, 3H) 1.46 (s, 9H), 1.23 (t, 3H, *J* = 7.6 Hz).

(*S*)-{1-[4-(4-Butyl-phenoxy)-phenylcarbamoyl]-2-hydroxy-1-methyl-ethyl}-carbamic acid *tert*-butyl ester



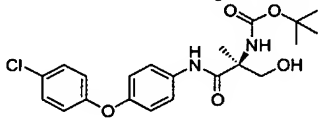
The final product was obtained as white solid following silica gel purification, in 45% yield, (0.092g). TLC (1:2 EtOAc:Hex), R_f = 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.45 (d, 2H, *J* = 9.2 Hz), 7.12 (d, 2H, *J* = 8.8 Hz), 6.96 (d, 2H, *J* = 8.8 Hz), 6.89 (d, 2H, *J* = 8.4 Hz), 4.07 (m, 1H), 3.59 (m, 1H), 2.58 (t, 2H, *J* = 7.6 Hz), 1.51-1.62 (m, 5H), 1.46 (s, 9H), 1.35 (m, 2H), 0.93 (t, 3H, *J* = 7.6 Hz).

(*S*)-{1-[4-(4-Butoxy-phenoxy)-phenylcarbamoyl]-2-hydroxy-1-methyl-ethyl}-carbamic acid *tert*-butyl ester



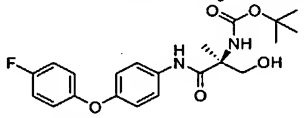
The final product was obtained as white solid following silica gel purification, in 25% yield, (0.023g). TLC (1:1 EtOAc:Hex), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.43 (d, 2H, *J* = 9.2 Hz), 6.90-6.94 (m, 4H), 6.85 (d, 2H, *J* = 9.2 Hz), 4.07 (m, 1H), 3.93 (t, 2H, *J* = 7.6 Hz) 3.58 (m, 1H), 1.74-1.78 (m, 2H), 1.58 (s, 3H), 1.50 (m, 2H), 1.46 (s, 9H), 0.98 (t, 2H, *J* = 7.2 Hz).

(*S*)-{1-[4-(4-chloro-phenoxy)-phenylcarbamoyl]-2-hydroxy-1-methyl-ethyl}-carbamic acid *tert*-butyl ester



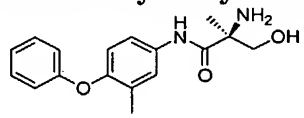
The final product was obtained as white solid following silica gel purification, in 53% yield, (0.107g). TLC (1:3 EtOAc:Hex), R_f = 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, 2H, J = 9.2 Hz), 7.26 (d, 2H, J = 8.8 Hz), 6.97 (d, 2H, J = 8.8 Hz), 6.90 (d, 2H, J = 8.8 Hz), 4.08 (m, 1H), 3.60 (d, 1H, J = 11.2 Hz), 1.59 (s, 3H), 1.47 (s, 9H).

(*S*)-{1-[4-(4-fluoro-phenoxy)-phenylcarbamoyl]-2-hydroxy-1-methyl-ethyl}-carbamic acid *tert*-butyl ester



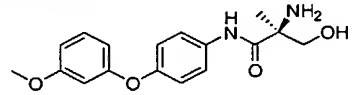
The final product was obtained as a hygroscopic solid following silica gel purification, in 33% yield, (0.063g). TLC (1:2 EtOAc:Hex), R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, 2H, J = 9.2 Hz), 6.99 (d, 2H, J = 8.0 Hz), 6.92-6.95 (m, 4H), 4.06 (m, 1H), 3.64 (d, 1H, J = 10.4 Hz), 1.58 (s, 3H), 1.46 (s, 9H).

(*S*)-2-Amino-3-hydroxy-2-methyl-N-(3-methyl-4-phenoxy-phenyl)-propionamide



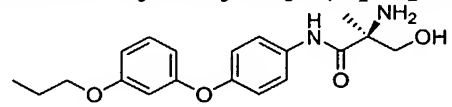
The final product was obtained as a white solid after HPLC, in 35% yield, (0.01g). MS (ESI, M+H$^+$) = 301.19; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), δ 7.25 (m, 1H), δ 7.2 (m, 3H,), 6.95 (t, 1H, J = 7.6 Hz), 6.75 (d, 2H, J = 8 Hz), 6.69 (d, 1H, J = 7.6), 4.13 (s, 1H), 3.92 (s, 1H), 2.05 (s, 3H), 1.52 (s, 3H).

(*S*)-2-Amino-3-hydroxy-N-[4-(3-methoxy-phenoxy)-phenyl]-2-methyl-propionamide



The final product was obtained as an off white solid following HPLC purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.18 (s, 2H), 7.63 (d, 2H, J = 8.8 Hz), 7.24 (t, 1H, J = 8.4 Hz), 7.02 (d, 2H, J = 9.2 Hz), 6.68 (m, 1H), 6.52 (t, 1H, J = 2.4 Hz), 6.48 (m, 1H), 3.98 (d, 1H, J = 11.6 Hz), 3.71 (s, 3H), 3.64 (d, 1H, J = 12.0 Hz), 1.48 (s, 3H).

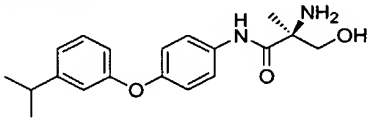
(*S*)-2-Amino-3-hydroxy-N-[4-(3-propoxy-phenoxy)-phenyl]-2-methyl-propionamide



The final product was obtained as an off white solid following HPLC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.14 (s, 2H), 7.63 (d, 2H, J = 9.2 Hz), 7.23 (t, 1H,

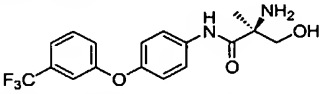
J = 8.4 Hz), 7.02 (d, 2H, J = 8.8 Hz), 6.67 (m, 1H), 6.48 (m, 2H), 5.79 (t, 1H, J = 4.8 Hz), 3.98 (dd, 1H, J = 4.8 and 11.6 Hz), 3.86 (t, 2H, J = 6.8 Hz), 3.63 (dd, 1H, J = 4.8 and 11.6 Hz), 1.68 (m, 2H), 1.48 (s, 3H) 0.93 (t, 3H, J = 7.2 Hz).

(*S*)-2-Amino-3-hydroxy-N-[4-(3-isopropyl-phenoxy)-phenyl]-2-methyl-propionamide



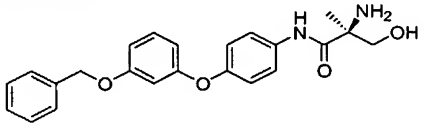
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 7.63 (d, 2H, J = 8.8 Hz), 7.28 (t, 1H, J = 8 Hz), 7.03 (m, 1H), 7.01 (m, 2H), 6.87 (t, 1H, J = 2.0 Hz), 6.74 (m, 1H), 3.98 (dd, 1H, J = 4.4 and 11.2 Hz), 3.62 (dd, 1H, J = 4.4 and 11.6 Hz), 3.09 (q, 1H, J = 7.6 and 14.8 Hz), 2.87 (m, 1H), 1.47 (s, 3H) 1.18 (d, 6H, J = 6.0 Hz).

(*S*)-2-Amino-3-hydroxy-N-[4-(3-trifluoromethyl-phenoxy)-phenyl]-2-methyl-propionamide



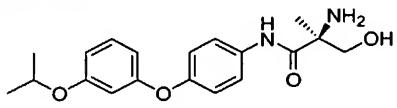
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 7.70 (d, 2H, J = 9.2 Hz), 7.47 (m, 1H), 7.26 (m, 2H), 7.14 (d, 2H, J = 9.2 Hz), 4.01 (dd, 1H, J = 4.0 and 11.2 Hz), 3.66 (dd, 1H, J = 4.0 and 11.6 Hz), 1.51 (s, 3H).

(*S*)-2-Amino-N-[4-(3-benzyloxy-phenoxy)-phenyl]-3-hydroxy-2-methyl-propionamide



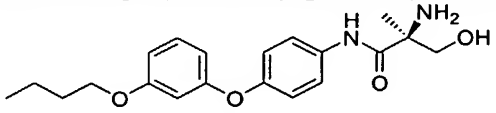
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.17 (s, 2H), 7.64 (d, 2H, J = 9.2 Hz), 7.41 (m, 2H), 7.38 (m, 1H), 7.35 (m, 1H), 7.27 (t, 1H, J = 8.0 Hz), 7.04 (d, 2H, J = 9.2 Hz), 6.78 (m, 1H), 6.61 (t, 1H, J = 2.4 Hz), 6.52 (m, 1H), 5.80 (t, 1H, J = 4.8 Hz), 5.08 (s, 2H), 4.00 (dd, 1H, J = 4.4 and 11.2 Hz), 3.65 (dd, 1H, J = 4.8 and 11.2 Hz), 1.49 (s, 3H).

(*S*)-2-Amino-3-hydroxy-N-[4-(3-isopropoxy-phenoxy)-phenyl]-2-methyl-propionamide



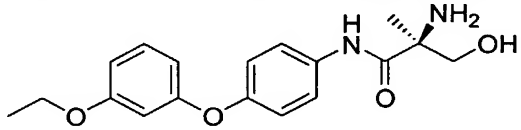
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 2H), 7.62 (d, 2H, J = 9.2 Hz), 7.22 (t, 1H, *J* = 8.8 Hz), 7.03 (d, 2H, J = 8.8 Hz), 6.65 (m, 1H), 6.47 (m, 2H), 5.76 (t, 1H, *J* = 4.4 Hz), 4.55 (m, 1H), 3.98 (dd, 1H, J = 5.2 and 12.0 Hz), 3.62 (dd, 1H, J = 4.8 and 12.0 Hz), 1.47 (s, 3H), 1.23 (s, 3H), 1.21 (s, 3H).

(*S*)-2-Amino-N-[4-(3-butoxy-phenoxy)-phenyl]- 3-hydroxy-2-methyl-propionamide



^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (d, 2H, J = 9.2 Hz), 7.23 (t, 1H, *J* = 8.4 Hz), 7.03 (d, 2H, J = 9.2 Hz), 6.66 (m, 1H), 6.48 (m, 2H), 5.75 (t, 1H, *J* = 4.4 Hz), 3.97 (dd, 1H, J = 5.2 and 11.2 Hz), 3.93 (t, 2H, J = 9.2 Hz), 3.62 (dd, 1H, J = 5.2 and 11.6 Hz), 1.65 (m, 2H), 1.47 (s, 3H), 1.39 (m, 2H), 0.90 (t, 3H, *J* = 7.2 Hz).

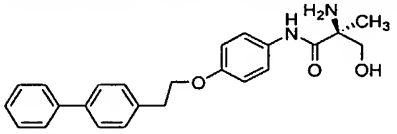
(*S*)-2-Amino-N-[4-(3-ethoxy-phenoxy)-phenyl]- 3-hydroxy-2-methyl-propionamide



^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (d, 2H, J = 8.8 Hz), 7.24 (t, 1H, *J* = 8.8 Hz), 7.03 (d, 2H, *J* = 9.2 Hz), 6.66 (m, 1H), 6.49 (m, 2H), 5.77 (t, 1H, *J* = 4.4 Hz), 3.96 (m, 3H), 3.63 (dd, 1H, *J* = 5.2 and 12.0 Hz), 1.467 (s, 3H), 1.28 (t, 3H, *J* = 7.2 Hz).

Example 5: Synthesis of Phenylamide Compounds with Arylalkoxy and Cycloalkylalkoxy Tail Groups

(A) (S)-2-amino-3-hydroxy-2-methyl-N-(4-(biphenethyloxy)phenyl) propanamide trifluoroacetic acid salt



1-(2-(4-nitrophenoxy)ethyl)biphenyl

2-biphenyl ethanol (1 g, 5 mmol), 4-nitrophenol (834 mg, 6 mmol), and triphenylphosphine (1.59 g, 6 mmol) was dissolved in 20 mL dichloromethane. The solution was chilled in an ice-water bath prior to the addition of diethylazodicarboxylate (949 µl, 6 mmol). The reaction was then stirred overnight, and the ice-water bath slowly warmed to room temperature. Crude product was purified by flash chromatography to yield 640 mg crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.1 (d), 7.6 (m), 7.47-7.41 (m), 7.34 (m), 7.17 (m), 4.39 (t, 2H), 3.13 (t, 2H).

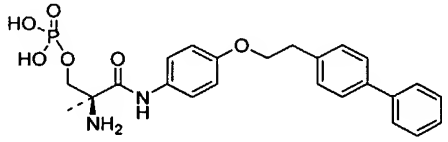
tert-butyl (S)-2-(4-(phenethyloxy)biphenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate

1-(2-(4-nitrophenoxy)ethyl)biphenyl (300 mg, 0.94 mmol) was dissolved in a mixture of absolute ethanol and ethyl acetate. The mixture was purged with nitrogen gas prior to the addition of 150 mg 10% Pd on carbon. The reaction was capped with a septum and stirred under 1 atm H_2 (g) overnight. Reaction was judged complete by TLC (R_f product ~ 0.5 in 1:1 EtOAc:hexanes). The solution was filtered through celite and the solvent evaporated under vacuum. Without further purification, the crude product was combined with *N*-(Boc)-α-methylserine (210 mg), HATU (364 mg), DIPEA (416 µl), and 10 mL DMF. The solution was stirred at room temperature for 3 hours. Solvent was removed by rotary evaporator and crude product purified by flash chromatography to yield 240 mg yellow liquid, 52% yield.

2-amino-3-hydroxy-2-methyl-N-(4-(phenethyloxy)biphenyl)propanamide trifluoroacetic acid salt

tert-butyl(S)-2-(4-(phenethyloxy)biphenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate (80 mg) was dissolved in a 1:1 mixture of 2 mL DCM:TFA for 3 hours. The title compound was purified by reverse phase chromatography and 29.6 mg white solid isolated as the TFA salt (in some cases reverse phase purification was not necessary). MS (ESI, $M+H^+$) = 391.2; ^1H NMR (400 MHz, DMSO-d_6) δ 7.65 (m), 7.60 (m), 7.52-7.40 (m), 6.93 (m), 4.197 (t, 2H), 3.8 (bm, 1H), 3.5 (bm, 1H), 3.06 (t, 2H), 1.38 (s, 3H).

(B) (S)-2-(4-(biphenethyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate



tert-butyl (S)-2-(4-(phenethyloxy)phenylcarbamoyl)-1-diethyl phosphatidylpropan-2-ylcarbamate

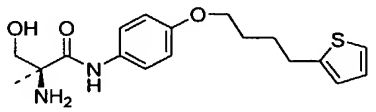
2-amino-3-hydroxy-2-methyl-N-(4-(phenethyloxy)biphenyl)propanamide trifluoroacetic acid salt (116 mg), diethylchloridophosphite (171 µl, 5 eq), and DIPEA (8eq) were combined in 2 ml anhydrous DCM under N_2 atmosphere. After 8 hours conversion to product remained low, ~20%, as judged by TLC (R_f~0.2 in 80% EtOAc:hexanes). More diethylchloridophosphite (171 µl, 5 eq) and DIPEA (8eq) were added to the reaction mixture and the solution stirred overnight. The next morning TLC

showed ~100% conversion to product. Flash chromatography yielded 10 mg of pure product (20% yield). MS (ESI, $M+Na^+$) = 649.

(S)-2-(4-(biphenethyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate.

(S)-2-(4-(phenethyloxy)phenylcarbamoyl)-2-aminopropyl diethyl phosphate (10 mg) was dissolved in 3 ml DCM, immersed in an ice bath, and excess trimethylsilylbromide added (20 eq). The reaction was monitored by liquid chromatography/mass spectrometry (LCMS). Complete disappearance of the starting material occurred overnight while stirring at room temperature. Solvent was evaporated and the crude product purified by reverse phase chromatography to yield 1.5 mg of the title compound (16% yield). MS (ESI, $M+H^+$) = 471.1; ^1H NMR (400 MHz, DMSO-d_6) δ 7.66-7.63 (m), 7.60-7.40 (m), 7.36 (m), 4.3 (m, 1H), 4.20 (t, 2H), 4.05 (bm, 1H), 3.051 (t, 2H), 1.48 (s).

(C) (S)-N-(4-(4-(thiophen-2-yl)butoxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide trifluoroacetic acid salt



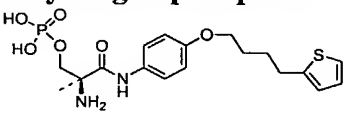
tert-butyl (S)-2-(4-(4-(thiophen-2-yl)butoxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate

This compound was synthesized from 2-(4-(4-nitrophenoxy)butyl)thiophene (280 mg), *N*-(Boc)-α-methylserine (205 mg), HATU (442 mg), and DIPEA (506 µl) following the procedure described in Example 5(A) to yield 280 mg product (62% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 7.44 (m, 2H), 7.29 (m, 1H), 6.9 (m, 1H), 6.84-6.81 (m, 3H), 5.00 (t, 1H), 3.93 (t, 2H), 3.61 (m, 2H), 2.84 (t, 2H), 1.73 (m, 4H), 1.48 (overlapping singlets, 9H).

(S)-N-(4-(4-(thiophen-2-yl)butoxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide trifluoroacetic acid salt.

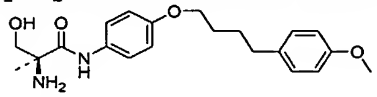
This compound was synthesized from tert-butyl (S)-2-(4-(4-(thiophen-2-yl)butoxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate (140 mg) according to the procedure provided in Example 5(A) to yield 31 mg white solid title compound. MS (ESI, $M+H^+$) = 349.5; ^1H NMR (400 MHz, DMSO-d_6) δ 9.79 (bs, 1H), 7.48 (m, 2H), 7.29 (m, 1H), 6.9-6.8 (m, 5H), 5.6 (bs, 1H), 3.95+3.8 (overlapping signals, 3H), 3.55 (m, 1H), 2.84 (m, 2H), 1.73 (m, 4H), 1.41 (s, 3H).

(D) (S)-2-(4-(4-(thiophen-2-yl)butoxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate



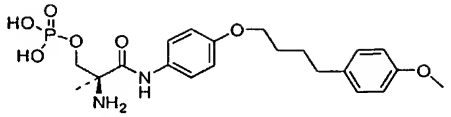
(S)-N-(4-(4-(thiophen-2-yl)butoxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide trifluoroacetic acid salt (116 mg), di(tert-butyl) diisopropylamidophosphite (143 mg, 163 µl), and 1H-tetrazole (108 mg) were combined in 3 ml anhydrous THF under N_2 (g) and stirred overnight. LCMS showed leftover starting material and more di(tert-butyl) diisopropylamidophosphite (143 mg, 163 µl), and 1H-tetrazole (108 mg) were added to the reaction mixture. The reaction was complete after several days stirring at room temperature. 264 ul of 30% aq H_2O_2 was then added to the solution and the reaction stirred for an additional 2.5 hours prior to quenching with 1 mL saturated sodium thiosulfite soln. The resulting mixture was diluted with EtOAc and the organic layer collected, concentrated, and purified by flash chromatography yielding 45 mg tert-butyl (S)-2-(4-(4-(thiophen-2-yl)butoxy)phenylcarbamoyl)-1-di-tert-butyl phosphatidylpropan-2-ylcarbamate. The purified sample was then dissolved in 2 mL 25% TFA:DCM and stirred for 1 hour. The solution was concentrated to yield 24 mg of the title compound. MS (ESI, $M+H^+$) = 429.2; ^1H NMR (400 MHz, DMSO-d_6) δ 9.8 (bs, 1H), 7.48 (m, 2H), 7.29 (m, 1H), 6.9-6.8 (m, 5H), 4.25 (m, 1H), 4.05 (m, 1H), 3.95 (bt, 3H), 3.55 (m, 1H), 2.84 (m, 2H), 1.73 (m, 4H), 1.41 (s, 3H).

(E) (S)-N-(4-(4-(4-methoxyphenyl)butoxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide trifluoroacetic acid salt



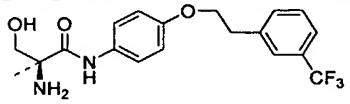
1-(4-(4-nitrophenoxy)butyl)-4-methoxybenzene (470 mg) was converted to 305 mg tert-butyl (S)-2-(4-(4-(4-methoxyphenyl)butoxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate following the general procedure provided in Example 5(A) employing *N*-(Boc)-α-methylserine (210 mg), HATU (360 mg), and DIPEA (860 ul). MS (ESI, $M+Na^+$) = 495.7. The carbamate (130 mg) was deprotected following the procedure in Example 5(A) yielding 108 mg of the title compound. MS (ESI, $M+H^+$) = 373.9.

(F) (S)-2-(4-(4-(4-methoxyphenyl)butoxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate



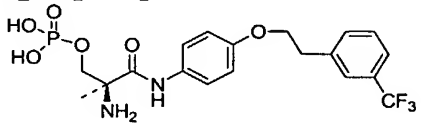
This compound was synthesized from (S)-N-(4-(4-(4-methoxyphenyl)butoxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide trifluoroacetic acid salt (115 mg) as described in Example 5(D) to yield 23 mg solid product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.9 (bs, 1H), 7.5 (d, 2H), 7.16 (d, 2H), 6.87 (d, 2H), 6.82 (d, 2H), 4.21 (m, 1H), 4.11 (m, 1H), 3.92 (m, 3H), 3.75 (s, 3H), 2.55 (m, 2H), 1.65 (m, 4H), 1.42 (s, 3H).

(G) (S)-N-(4-(3-(trifluoromethyl)phenethyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide trifluoroacetic acid salt.



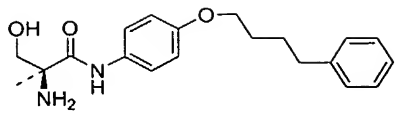
1-(3-(trifluoromethyl)phenethyloxy)-4-nitrobenzene (470 mg) was converted to 290 mg tert-butyl (S)-2-(4-(3-(trifluoromethyl)phenethyloxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate following the general procedure provided in Example 5(A) employing *N*-(Boc)-α-methylserine (210 mg), HATU (360 mg), and DIPEA (900 µl). MS (ESI, M+H$^+$) = 483.4. The carbamate (145 mg) was deprotected following the procedure in Example 5(A) yielding 143 mg of the title compound. MS (ESI, M+H$^+$) = 383.1. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.8 (bs, 1H), 7.67-7.40 (m, 6H), 6.88 (m, 2H), 5.67 (bs, 1H), 4.18 (t, 3H), 3.91 (m, 1H), 3.58 (m, 1H), 3.11 (t, 3H), 1.41 (s, 3H).

(H) (S)-2-(4-(3-(trifluoromethyl)phenethyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate.



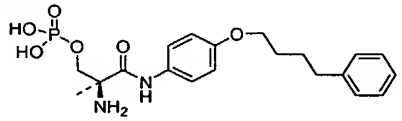
This compound was synthesized from (S)-N-(4-(3-(trifluoromethyl)phenethyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide trifluoroacetic acid salt (124 mg) as described for Example 5(D) to yield 50 mg solid product. MS (ESI, M+H$^+$) = 463.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (bs, 1H), 7.68-7.49 (m, 6H), 6.90 (m, 2H), 4.18 (t, 3H), 4.05 (m, 2H), 3.11 (t, 3H), 1.41 (s, 3H).

(I) (S)-N-(4-(4-phenylbutoxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide trifluoroacetic acid salt



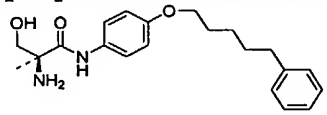
1-(4-phenylbutoxy)-4-nitrobenzene (730 mg) was converted to 305 mg tert-butyl (S)-2-(4-(4-phenylbutoxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate following the general procedure provided in Example 5(A) employing *N*-(Boc)-α-methylserine (210 mg), HATU (360 mg), and DIPEA (860 µl). MS (ESI, $M+Na^+$) = 465.5. The carbamate (152 mg) was deprotected following the procedure in AS1-C yielding 111 mg of the title compound. MS (ESI, $M+H^+$) = 343.9.

(J) (S)-2-(4-(4-phenylbutoxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate



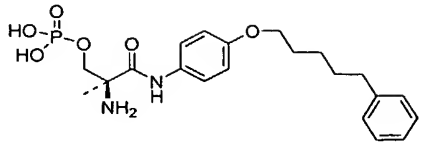
This compound was synthesized from (S)-N-(4-(4-phenylbutoxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide trifluoroacetic acid salt (120 mg) in a manner similar to that provided in Example 5(D) to yield 40 mg solid product. MS (ESI, $M+H^+$) = 423.7; ^1H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 7.47 (d, 6H), 7.27-7.13 (m, 5H), 6.88 (m, 2H), 4.21 (t, 1H), 4.06 (m, 1H), 3.94 (t, 2H), 2.64 (m, 2H), 1.7 (m, 4H), 1.44 (s, 3H).

(K) (S)-N-(4-(5-phenylpentyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide trifluoroacetic acid salt



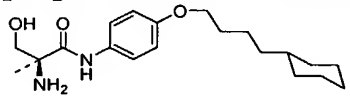
1-(5-phenylpentyloxy)-4-nitrobenzene (560 mg) was converted to 260 mg tert-butyl (S)-2-(4-(5-phenylpentyloxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate following the general procedure outlined in Example 5(A) employing *N*-(Boc)-α-methylserine (210 mg), HATU (360 mg), and DIPEA (860 µl). MS (ESI, $M+Na^+$) = 357.8. The carbamate (150 mg) was deprotected following the procedure in Example 5(A) yielding 147 mg of the title compound. MS (ESI, $M+H^+$) = 357.8.

(L) (S)-2-(4-(5-phenylpentyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate



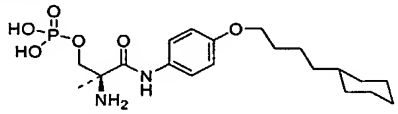
This compound was synthesized from (S)-N-(4-(5-phenylpentyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide (117 mg) as described in Example 5(D) to yield 66 mg solid product. MS (ESI, $M+H^+$) = 437.5; ^1H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 7.48 (m, 2H), 7.23 (m, 2H), 7.16 (m, 2H), 6.88 (m, 2H), 4.27 (t, 1H), 4.07 (m, 1H), 3.92 (t, 2H), 2.57 (t, 2H), 1.7 (m, 2H), 1.65 (m, 2H), 1.5 (s, 3H), 1.42 (m, 2H).

(M) (S)-N-(4-(4-cyclohexylbutoxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide trifluoroacetic acid salt



1-(4-cyclohexylbutoxy)-4-nitrobenzene (1 g) was converted to 260 mg tert-butyl (S)-2-(4-(4-cyclohexylbutoxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate following the general procedure outlined in Example 5(A) employing *N*-(Boc)-α-methylserine (210 mg), HATU (360 mg), and DIPEA (860 µl). MS (ESI, $M+Na^+$) = 449. The carbamate (87 mg) was deprotected following the procedure in Example 5(A) yielding 81 mg of the title compound. MS (ESI, $M+H^+$) = 349.5. ^1H NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 1H), 7.47 (m, 2H), 6.88 (m, 2H), 5.65 (m, 1H), 4.27 (overlapping signals, 3H), 3.6 (m, 1H), 1.6 (m, 6H), 1.4 (m, 5H), 1.15 (m, 6H), 0.85 (m, 3H).

(N) (S)-2-(4-(4-cyclohexylbutoxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate



This compound was synthesized from (S)-N-(4-(4-cyclohexylbutoxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide trifluoroacetic acid salt (173 mg) as described in Example 5(D) to yield 27 mg solid product. MS (ESI, $M+H^+$) = 429; ^1H NMR (400 MHz, DMSO-d_6) δ 9.8 (bs, 1H), 7.47 (m, 2H), 6.88 (m, 2H), 4.15 (m, 1H), 4.02 (m, 1H), 3.90 (t, 2H), 1.68 (m, 6H), 1.4 (m, 5H), 1.15 (m, 6H), 0.85 (m, 3H).

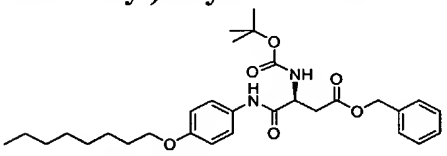
Example 6: Synthesis of Carboxylic Acid Compounds

General method for acylation of substituted 4-aminophenol

To a solution of N-(Boc)-α-methylserine (1.0 equiv) in DMF (10 mL) was added DIPEA (3.0 equiv) and HATU (1.2 equiv), followed by the addition of 4-aminophenol (1.0 equiv.). The reaction mixture was stirred at room temperature under an atmosphere

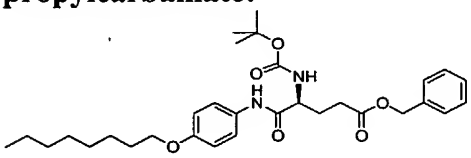
of nitrogen for 12-24 hours. The reaction was then diluted with EtOAc (25 mL) and washed with 10% NH_4Cl (2 x 25 mL), 5% $NaHCO_3$ (2 x 25 mL), and saturated NaCl (1 x 25 mL). The organic layer was dried over anhydrous $MgSO_4$ then the solvent removed in vacuo. The crude product was purified using silica gel column chromatography.

tert-Butyl (S)-2-((benzyloxy)carbonyl)-1-(4 (octyloxy)phenyl-carbamoyl)ethylcarbamate



The product was obtained as a yellow solid in 94% (2.34 g) yield. TLC (1:2 EtOAc:Hex), $R_f = 0.6$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (br s, 1H), 7.30-7.38 (m, 7H), 6.83 (d, 2H, J = 9.0 Hz), 5.80 (br s, 1H), 5.18 (d, 1H, J = 12.5 Hz), 5.13 (d, 1H, J = 12.5 Hz), 4.62 (br s, 1H), 3.92 (t, 2H, J = 6.6 Hz), 3.05-3.13 (m, 1H), 2.75-2.83 (m, 1H), 1.72-1.81 (m, 2H), 1.23-1.50 (m, 10H), 1.47 (s, 9H), 0.89 (t, 3H, J = 7.0 Hz).

tert-Butyl (S)-3-((benzyloxy)carbonyl)-1-(4-(octyloxy)phenylcarbamoyl) propylcarbamate:

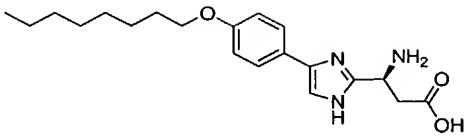


The product was obtained as a yellow solid in 94% (2.28 g) yield. TLC (1:2 EtOAc:Hex), $R_f = 0.6$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (br s, 1H), 7.31-7.40 (m, 7H), 6.84 (d, 2H, J = 8.9 Hz), 5.30 (br s, 1H), 5.10-5.19 (m, 2H), 4.25 (br s, 1H), 3.92 (t, 2H, J = 6.7 Hz), 2.60-2.70 (m, 1H), 2.45-2.56 (m, 1H), 2.13-2.28 (m, 1H), 1.95-2.06 (m, 1H), 1.72-1.80 (m, 2H), 1.23-1.48 (m, 10H), 1.45 (s, 9H), 0.89 (t, 3H, J = 6.9 Hz).

General method for deprotection of Cbz-amino acids

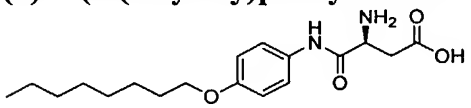
To a solution of Boc-protected amino acid ester (1.0 equiv) in MeOH at room temperature was added 10% Pd on carbon (0.1 equiv by mass) and stirred under H_2 atmosphere for 6-18 hours. The solution was then filtered through Celite to remove Pd and Carbon. The filtrated was evaporated to dryness. The residue was then dissolved in CH_2Cl_2 and TFA (2:1) and stirred at room temperature 2 hours to remove the Boc protecting group. The solvent was then evaporated to dryness under reduced pressure. The final product was purified by prep HPLC as necessary.

(S)-3-amino-3-(4-(4-(octyloxy)phenyl)-1H-imidazol-2-yl)propanoic acid:



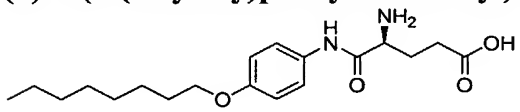
The product was obtained as a white solid in 95% (65 mg) yield. MS (ESI, $M+H^+$) = 360.17; ^1H NMR (400 MHz, DMSO-d_6) δ 8.42 (br s, 3H), 7.64 (d, 2H, J = 8.8 Hz), 7.48 (s, 1H), 6.93 (d, 2H, J = 8.8), 4.64 (br t, 1H, J = 6.4 Hz), 3.94 (t, 2H, J = 6.8 Hz), 3.12 (dd, 1H, J = 17.2 Hz, J = 6.8 Hz), 2.94 (dd, 1H, J = 17.2 Hz, J = 6.8 Hz), 1.64-1.75 (m, 2H), 1.20-1.45 (m, 10H), 0.85 (t, 3H, J = 7.2 Hz).

(S)-3-(4-(octyloxy)phenylcarbamoyl)-3-aminopropanoic acid:



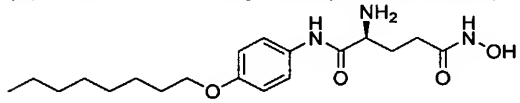
The product was obtained as a white solid in 99% (175 mg) yield. MS (ESI, $M+H^+$) = 337.36; ^1H NMR (400 MHz, DMSO-d_6) δ 10.30 (br s, 1H), 8.26 (br s, 3H), 7.45 (d, 2H, J = 9.0 Hz), 6.88 (d, 2H, J = 9.0 Hz), 4.18-4.24 (br s, 1H), 3.90 (t, 2H, J = 6.3 Hz), 2.74-2.98 (m, 2H), 1.60-1.76 (m, 2H), 1.16-1.45 (m, 10H), 0.85 (t, 3H, J = 7.0 Hz).

(S)-4-(4-(octyloxy)phenylcarbamoyl)-4-aminobutanoic acid:



The product was obtained as a white solid in 99% (150 mg) yield. MS (ESI, $M+H^+$) = 351.40; ^1H NMR (400 MHz, DMSO-d_6) δ 10.30 (br s, 1H), 7.45 (d, 2H, J = 9.2 Hz), 6.89 (d, 2H, J = 9.2 Hz), 3.85-3.95 (m, 3H), 2.35 (t, 2H, J = 7.0 Hz), 1.96-2.06 (m, 2H), 1.62-1.72 (m, 2H), 1.18-1.43 (m, 10H), 0.84 (t, 3H, J = 7.0 Hz).

(S)-2-amino-N^5-hydroxy-N^1-(4-(octyloxy)phenyl)pentanediamide:

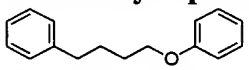


The Boc-protected carboxylate intermediate from previous step was coupled with hydroxylamine hydrochloride using general HATU coupling conditions. After TFA deprotection of Boc group the final compound was purified by prep HPLC as a white solid in 20% (12 mg) yield. MS (ESI, $M+H^+$) = 366.48; ^1H NMR (400 MHz, DMSO-d_6) δ 10.53 (br s, 0.5H), 10.31 (br s, 0.5H), 9.86 (br s, 0.5H), 8.80 (br s, 0.5H), 8.22 (br s, 2H), 7.85 (br s, 1H), 7.40-7.53 (m, 2H), 6.83-6.93 (m, 2H), 4.10-4.16 (m, 1H), 3.86-3.94 (m, 2H), 1.80-2.25 (m, 4H), 1.54-1.74 (m, 2H), 1.18-1.45 (m, 10H), 0.86 (t, 3H, J = 6.6 Hz).

Example 7: General Procedure for Synthesis of Aryl-Alkoxy Ethers Under Mitsunobu Conditions

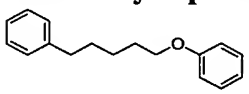
Phenol (1.2 equiv) and triphenyl phosphine (1.2 equiv) were added to an ice cold solution of the substituted phenyl alcohols (1.0 equiv) in DCM. To this mixture on ice was added DEAD or DIAD drop-wise while maintaining the temperature of the reaction mixture under 5 °C. The reaction mixture was then allowed to gradually warm to room temperature and stirred overnight. The organic layer was extracted with water, 10% NH_4Cl and then brine. The combined organic layer was dried with $MgSO_4$ and the solvent evaporated under reduced pressure to give yellow oil which was purified by silica-gel chromatography, EtOAc-Hexane gradient. The fractions corresponding to the product were pooled and the solvent removed *in vacuo* to give the desired product.

1-Phenoxy-4-phenyl butane:



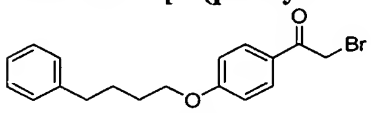
The final product was obtained as yellow oil after column chromatography, in 67% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 4H), 7.18 (m, 3H), 6.91 (m, 3H), 3.96 (t, 2H, J = 6.0 Hz), 2.68 (t, 2H, J = 6.8 Hz), 1.82 (m, 4H).

1-Phenoxy-5-phenyl pentane:



The final product was obtained as oil after column chromatography, in 37% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 4H), 7.18 (d, 3H, J = 7.2 Hz), 6.93 (dd, 1H, J = 1.0 and 6.8 Hz), 6.88 (m, 2H), 3.94 (t, 2H, J = 6.4 Hz), 2.64 (t, 2H, J = 8.0 Hz), 1.81 (m, 2H), 1.69 (m, 2H), 1.52 (m, 2H).

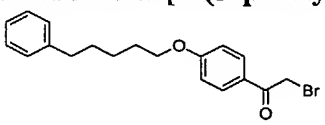
2-Bromo-1-[4-(phenyl-butoxy)phenyl]-ethanone:



The final product was obtained as a white solid after column chromatography, in 25% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, 2H, J = 8.4 Hz), 7.33-7.25 (m, 4H), 6.87-

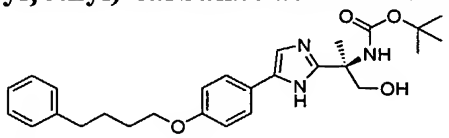
6.95 (m, 3H), 4.43 (s, 2H), 3.97 (t, 2H, J = 5.6 Hz), 2.76 (t, 2H, J = 7.6 Hz), 1.82 (m, 4H).

2-Bromo-1-[4-(5-phenyl-pentyloxy)phenyl]-ethanone:



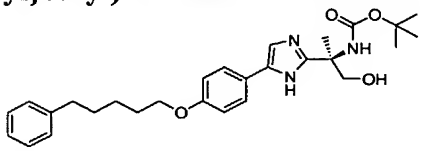
The final product was obtained as a white solid after column chromatography, in 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 2H, J = 8.4 Hz), 7.24-7.30 (m, 4H), 7.18 (d, 2H, J = 6.4 Hz), 6.86-6.89 (m, 2H), 4.43 (s, 2H), 3.94 (t, 2H, J = 6.4 Hz), 2.71 (t, 1H, J = 7.6 Hz), 2.64 (t, 1H, J = 7.6 Hz), 1.81 (m, 2H), 1.69 (m, 2H), 1.51 (m, 2H).

(*R*)-(2-Hydroxy-1-methyl-1-{5-[4-(4-phenyl-butoxy)-phenyl]-1*H*-imiazol-2-yl}ethyl)-carbamic acid tert-butyl ester:



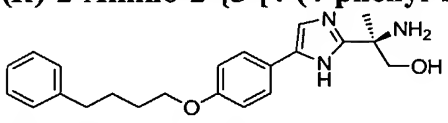
The final product was obtained as yellow oil after column chromatography, in 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.26 (m, 4H), 7.21 (m, 2H), 7.17 (s, 1H), 6.87-6.94 (m, 2H), 4.33 (d, 1H, J = 11.6 Hz), 3.97 (t, 2H, J = 5.6 Hz), 3.35 (d, 1H, J = 12.0 Hz), 2.69 (t, 2H, J = 7.2 Hz), 2.53 (s, 2H), 1.82 (m, 4H), 1.67 (s, 3H), 1.44 (s, 9H).

(*R*)-(2-Hydroxy-1-methyl-1-{5-[4-(5-phenyl-pentyloxy)-phenyl]-1*H*-imiazol-2-yl}ethyl)-carbamic acid tert-butyl ester:



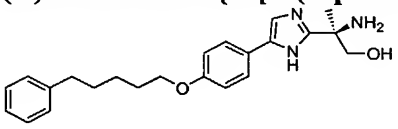
The final product was obtained as yellow oil after column chromatography, in 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 2H, J = 7.2Hz), 7.24-7.28 (m, 2H), 7.17 (d, 2H, J = 8.0Hz), 7.13 (s, 1H), 6.86-6.89 (m, 2H), 5.77 (s, 1H), 4.27 (d, 1H, J = 11.2 Hz), 3.94 (t, 2H, J = 6.4 Hz), 3.64 (d, 1H, J = 11.6 Hz), 2.63 (t, 2H, J = 7.6 Hz), 1.81 (m, 2H), 1.69 (m, 2H), 1.66 (s, 3H), 1.42 (s, 9H), 1.26 (m, 2H).

(*R*)-2-Amino-2-{5-[4-(4-phenyl-butoxy)-phenyl]-1*H*-imiazol-2-yl}-propan-1-ol:



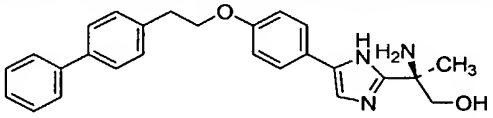
The compound was obtained as a white solid after HPLC purification. Yield: 50 %, (60mg). MS (ESI, M+H$^+$) = 366.3

(*R*)-2-Amino-2-{5-[4-(5-phenyl-pentyloxy)-phenyl]-1*H*-imiazol-2-yl}-propan-1-ol:



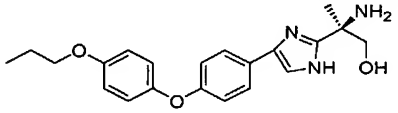
The compound was obtained as a white solid after HPLC purification. Yield: 49 %, (60mg). MS (ESI, $M+H^+$) = 380.3

(*R*)-2-Amino-2-(5-(4-(biphenylethyloxy)phenyl)-1*H*-imidazol-2-yl)propan-1-ol:



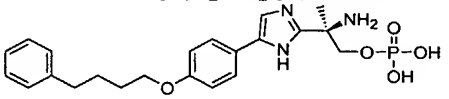
MS (ESI, $M+H^+$) = 414; ^1H NMR (400 MHz, DMSO-d_6) δ 8.4 (bs, 2H), 7.7 (m, 4H), 7.5 (m, 4H), 7.3 (d, 3H), 6.9 (d, 2H), 5.7 (bs), 4.18 (t, 2H), 3.7 (d, 1H), 3.6 (d, 1H), 3.04 (t, 2H), 1.45 (s, 3H).

(*R*)-2-Amino-2-{4-[4-(4-propoxy-phenoxy)-phenyl]-1*H*-imiazol-2-yl}-propan-1-ol:



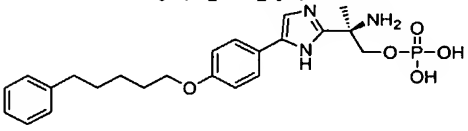
The compound was obtained as a white solid after HPLC purification. Yield: 60 %, (10mg). MS (ESI, $M+H^+$) = 367.5

(*R*)-Phosphoric acid mono-(2-amino-2-{5-[4-(4-phenyl-butoxy)-phenyl]-1*H*-imidazol-2-yl}-propyl) ester:



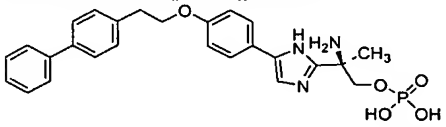
The compound was obtained as a white solid after HPLC purification. Yield: 32 %, (25mg). MS (ESI, $M+H^+$) = 446.4

(*R*)-Phosphoric acid mono-(2-amino-2-{5-[4-(4-phenyl-pentyloxy)-phenyl]-1H-imidazol-2-yl}-propyl) ester:



The compound was obtained as a white solid after HPLC purification. Yield: 39 %, (41mg). MS (ESI, $M+H^+$) = 459.2

(*R*)-2-Amino-2-(5-(4-(biphylenethyloxy)phenyl)-1*H*-imidazol-2-yl)propyl dihydrogen phosphate:

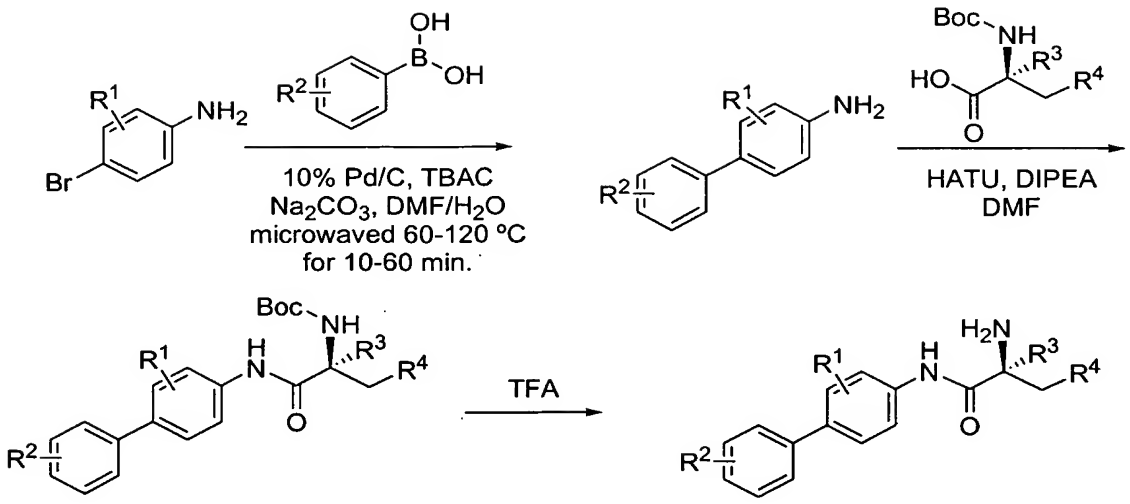


This compound was synthesized from *tert*-butyl (*R*)-1-hydroxy-2-(5-(4-(biphenylethyloxy)phenyl)-1*H*-imidazol-2-yl)propan-2-ylcarbamate (46 mg) to yield 9.2 mg solid product. MS (ESI, $M+H^+$) = 494; ^1H NMR (400 MHz, DMSO-d_6) δ 9.4 (s), 8.2 (s, 1H), 7.7 (m, 6H), 7.5 (m, 5H), 7.3 (m, 1H), 6.9 (d, 2H), 5.7 (br s), 4.25 (t, 2H), 4.15 (t, 2H), 4.05 (m, 1H), 3.9 (q, 1H), 3.1 (t, 2H), 1.45 (s, 3H).

Example 8: Synthesis in Biphenyl Amide Series

Several biphenyls were synthesized using the process described in Scheme 7. Microwave assisted Suzuki cross-coupling of substituted aryl boronic acids with substituted anilines afforded good to excellent yields of the biaryl amine intermediates. Furthermore, the acylation of the substituted biaryl amines with the desired headpiece followed by deprotection of the Boc group afforded the final compounds.

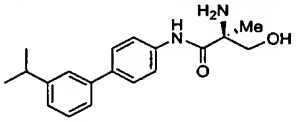
Scheme 7.



General procedure for Suzuki cross-coupling:

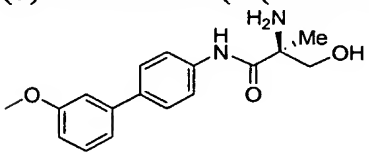
To a mixture of a substituted bromoaniline (1.0 equiv), substituted aryl boronic acid (1.2 equiv), 10% Pd on carbon (0.1 equiv), tetrabutylammonium chloride (0.1 equiv), and sodium carbonate (1.0 equiv), in a microwave tube was added a 1:1 mixture of DMF:H_2O. The mixture was then heated to 70 °C for 20-60 minutes using a microwave. The reaction was then diluted with EtOAc (25 mL) and washed with H_2O (2 x 25 mL) then the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography using Combi-Flash system (Hex:EtOAc) as required.

(*S*)-2-Amino-*N*-(4-(3-isopropylphenyl)phenyl)-3-hydroxy-2-methylpropanamide:



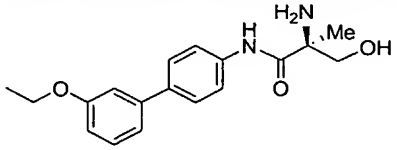
MS (ESI, M+H$^+$) = 313.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (br s, 1H), 8.18 (br s, 2H), 7.63-7.74 (m, 4H), 7.41-7.51 (m, 2H), 7.35 (t, 1H, J = 7.6 Hz), 7.21 (d, 1H, J = 7.6 Hz), 5.79 (t, 1H, J = 4.8 Hz), 4.00 (dd, 1H, J = 11.6 Hz, J = 4.8 Hz), 3.65 (dd, 1H, J = 11.6 Hz, J = 5.2 Hz), 2.86-3.02 (m, 1H), 1.50 (s, 3H), 1.24 (d, 6H, J = 7.6 Hz).

(*S*)-2-Amino-*N*-(4-(3-methoxyphenyl)phenyl)-3-hydroxy-2-methylpropanamide:



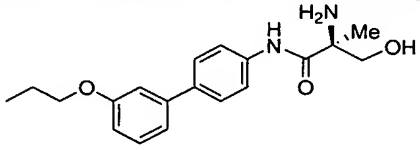
MS (ESI, M+H$^+$) = 301.7; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (br s, 1H), 8.19 (br s, 2H), 7.55-7.64 (m, 4H), 7.34 (t, 1H, J = 7.6 Hz), 7.16-7.24 (m, 2H), 6.88-6.94 (m, 1H), 5.80 (br s, 1H), 4.00 (dd, 1H, J = 11.6 Hz, J = 4.8 Hz), 3.80 (s, 3H), 3.64 (dd, 1H, J = 11.6 Hz, J = 5.2 Hz), 1.50 (s, 3H).

(*S*)-2-Amino-*N*-(4-(3-ethoxyphenyl)phenyl)-3-hydroxy-2-methylpropanamide:



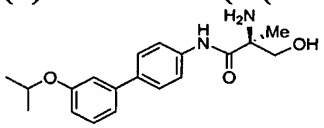
MS (ESI, M+H$^+$) = 315.6; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.97 (br s, 1H), 8.18 (br s, 2H), 7.64-7.73 (m, 4H), 7.33 (t, 1H, J = 7.6 Hz), 7.14-7.23 (m, 2H), 6.86-6.91 (m, 1H), 5.80 (br s, 1H), 4.08 (q, 2H, J = 7.2 Hz), 4.00 (dd, 1H, J = 11.6 Hz, J = 4.8 Hz), 3.64 (dd, 1H, J = 11.6 Hz, J = 5.2 Hz), 1.50 (s, 3H), 1.33 (t, 3H, J = 7.2 Hz).

(*S*)-2-Amino-*N*-(4-(3-propoxyphenyl)phenyl)-3-hydroxy-2-methylpropanamide:



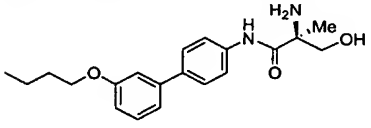
MS (ESI, M+H$^+$) = 329.7; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.96 (br s, 1H), 8.18 (br s, 2H), 7.64-7.74 (m, 4H), 7.33 (t, 1H, J = 7.6 Hz), 7.13-7.22 (m, 2H), 6.86-6.92 (m, 1H), 5.80 (br t, 1H, J = 4.5 Hz), 4.00 (dd, 1H, J = 11.6 Hz, J = 4.8 Hz), 3.98 (t, 2H, J = 7.2 Hz), 3.65 (dd, 1H, J = 11.6 Hz, J = 5.2 Hz), 1.68-1.80 (m, 2H), 1.50 (s, 3H), 1.00 (t, 3H, J = 7.2 Hz).

(*S*)-2-Amino-*N*-(4-(3-isopropoxyphenyl)phenyl)-3-hydroxy-2-methylpropanamide:



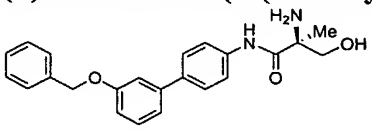
MS (ESI, M+H$^+$) = 329.8; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.96 (br s, 1H), 8.18 (br s, 2H), 7.62-7.73 (m, 4H), 7.32 (t, 1H, J = 7.6 Hz), 7.11-7.20 (m, 2H), 6.86-6.92 (m, 1H), 5.80 (br t, 1H, J = 4.5 Hz), 4.55-4.80 (m, 1H), 4.00 (dd, 1H, J = 11.6 Hz, J = 4.8 Hz), 3.65 (dd, 1H, J = 11.6 Hz, J = 5.2 Hz), 1.50 (s, 3H), 1.28 (d, 6H, J = 7.2 Hz).

(*S*)-2-Amino-*N*-(4-(3-*n*-butoxyphenyl)phenyl)-3-hydroxy-2-methylpropanamide:



MS (ESI, M+H$^+$) = 343.5; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.97 (br s, 1H), 8.18 (br s, 2H), 7.64-7.74 (m, 4H), 7.33 (t, 1H, J = 7.6 Hz), 7.13-7.22 (m, 2H), 6.86-6.92 (m, 1H), 5.79 (br t, 1H, J = 4.5 Hz), 4.03 (t, 2H, J = 7.2 Hz), 4.00 (dd, 1H, J = 11.6 Hz, J = 4.8 Hz), 3.64 (dd, 1H, J = 11.6 Hz, J = 5.2 Hz), 1.65-1.75 (m, 2H), 1.50 (s, 3H), 1.49-1.52 (m, 2H), 0.92 (t, 3H, J = 7.2 Hz).

(*S*)-2-Amino-*N*-(4-(3-benzyloxyphenyl)phenyl)-3-hydroxy-2-methylpropanamide:

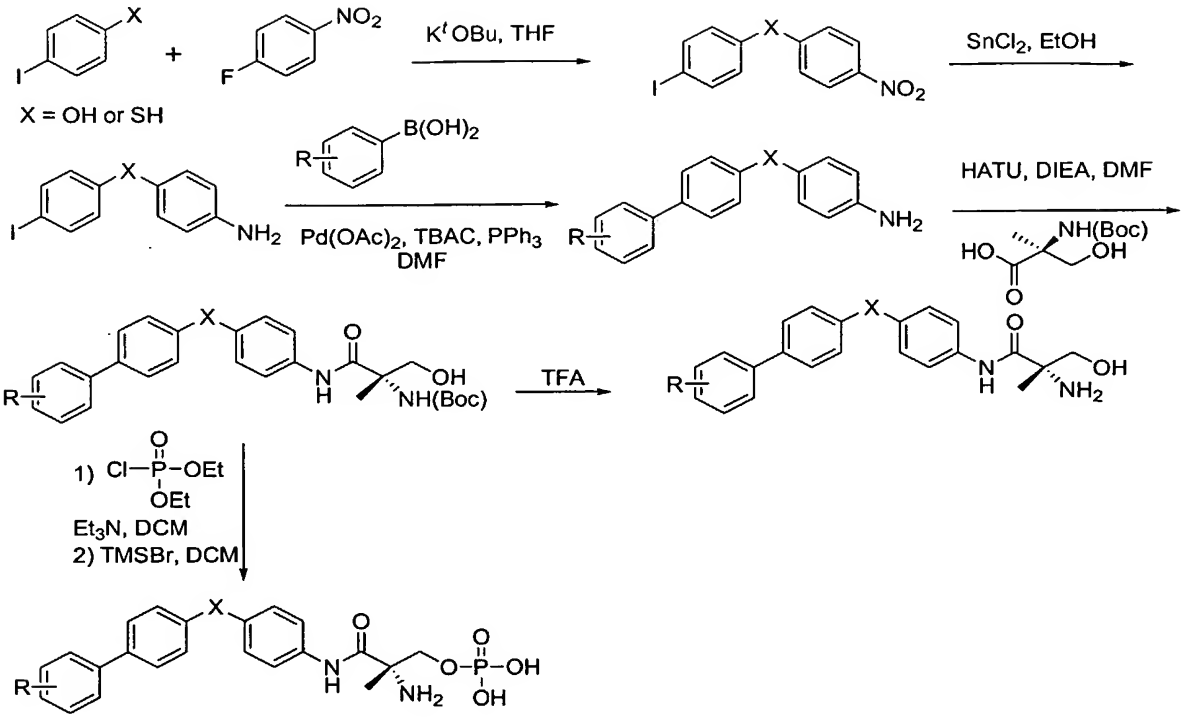


MS (ESI, $M+H^+$) = 377.5; ^1H NMR (400 MHz, DMSO-d_6) δ 9.96 (br s, 1H), 8.18 (br s, 2H), 7.64-7.74 (m, 4H), 7.44-7.82 (m, 2H), 7.29-7.42 (m, 6H), 6.96-7.00 (m, 1H), 5.79 (br t, 1H, J = 4.5 Hz), 5.17 (s, 2H), 4.00 (dd, 1H, J = 11.6 Hz, J = 4.8 Hz), 3.64 (dd, 1H, J = 11.6 Hz, J = 5.2 Hz), 1.50 (s, 3H).

Example 9: General Procedure for Synthesis of Substituted Biaryl Ether/Thioether Analogs

The 4-iodophenyl-4-nitrophenoxy ethers were synthesized by reacting 4-iodophenol with 4-fluoro-nitrobenzene in the presence of a base K^{t}OBu in THF at 50 °C (Scheme 2). The nitro group was reduced using $SnCl_2$ in EtOH at 70 °C, followedSuzuki cross-coupling then acylation of the amine with L-(Boc)-α-Me-Ser-OH using HATU. The Boc- group can then be removed using TFA in DCM or the protected material is used to synthesize the phosphate before deprotection.

Scheme 8.



General procedure forthe synthesis of 4-(4-iodophenoxy)-nitrobenzene:

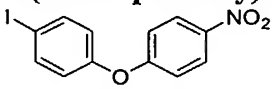
To a THF solution of 4-iodophenol (1.0g, 1.0equiv) is added K'OBu (1.0M in THF, 1.0 equiv). The solution is stirred at room temperature for approximately 5 minutes and then a solution of 4-fluoro-nitrobenzene (1.1 equiv) is added dropwise. The reaction mixture is then heated to 50 °C using an oil bath and the reaction progress monitored by TLC (EtOAc : Hexane, 0.5:9.5). The reaction is complete when no more 4-iodophenol is detected by TLC. The reaction is then cooled to room temperature and put in an ice bath. Water is added slowly to quench the unreacted base, followed by extraction of the product into EtOAc. The organic layer is then washed with 10% NH4Cl and brine, dried over MgSO4, and then solvent removed under reduced pressure. The crude product is purified using Combi-Flash silica gel column chromatography, using a Hexane/EtOAc gradient. The fractions corresponding to the product are pooled and the solvent removed in vacuo to give a yellow solid (Scheme 2).

General procedure for synthesis of substituted 4-biayloxy aniline:

To a DMF solution of the 4-(haloaryloxy)-aniline (1.0 equiv) and substituted aryl boronic acid in a microwave tube, was added $Pd(OAc)_2$ (0.1 equiv), triphenyl phosphine (0.2 equiv), cesium carbonate (1.0-2.0 equiv) and TBAC (0.1 equiv). The reaction was then sealed and heated at 70 °C for 3-18 hours using an oil bath. The reaction mixture was filtered through a bed of Celite and then diluted with EtOAc (25 mL), washed with water (2 x 10 mL) and then brine (1 x 10 mL). The organic layer was then dried over

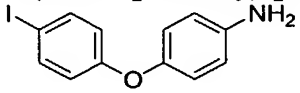
$MgSO_4$, and then was solvent removed under reduced pressure. The crude product was purified using Combi-Flash silica gel column chromatography, using a Hexane/EtOAc gradient.

4-(4-Iodophenoxy)-nitrobenzene:



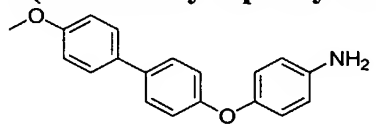
The final product was obtained as a yellow solid after purification in 73% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 8.21(d, 2H, J = 8.6 Hz), 7.73(d, 2H, J = 8.8 Hz), 7.02 (d, 2H, J = 9.2 Hz), 6.86 (d, 2H, J = 8.8 Hz).

4-(4-Iodophenoxy)-phenylamine:



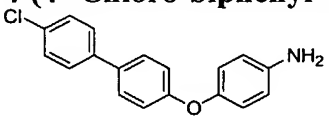
The final product was obtained as a brown solid after purification in 45% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, 2H, J = 8.8 Hz), 6.84 (d, 2H, J = 8.4 Hz), 6.66–6.70 (m, 4H).

4-(4'-Methoxy-biphenyl-4-yloxy)-phenylamine:



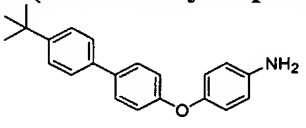
The final product was obtained as an off white solid after purification in 95% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.48 (m, 4H), 6.94-6.98 (m, 4H), 6.90 (d, 2H, J = 8.4 Hz), 6.69 (d, 2H, J = 8.8 Hz), 3.84 (s, 3H).

4-(4'-Chloro-biphenyl-4-yloxy)-phenylamine:



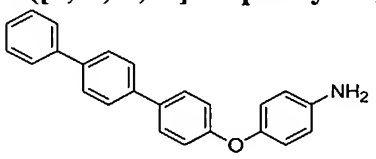
The final product was obtained as an off white solid after purification in 90% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.47 (m, 4H), 7.37 (d, 2H, J = 6.4 Hz), 6.97 (d, 2H, J = 8.8 Hz), 6.90 (d, 2H, J = 8.8 Hz), 6.70 (d, 2H, J = 8.8 Hz).

4-(4'-*tert*-Butyl-biphenyl-4-yloxy)-phenylamine:



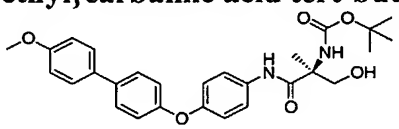
The final product was obtained as an off white solid after purification in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.50 (m, 6H), 6.98 (d, 2H, J = 8.8 Hz), 6.91 (d, 2H, J = 8.0 Hz), 6.70 (d, 2H, J = 8.0 Hz), 1.37 (s, 9H).

4-([1,1',4',1"]Terphenyl-4-yloxy)-phenylamine:



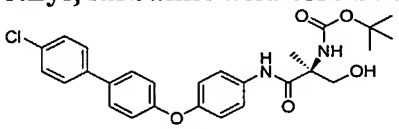
The final product was obtained as an off white solid after purification in 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, 1H, J = 7.2 Hz), 7.77 (d, 2H, J = 8.0 Hz), 7.70 (d, 2H, J = 7.2 Hz), 7.63-7.64 (m, 4H), 7.55 (d, 2H, J = 8.4 Hz), 7.01 (d, 2H, J = 8.8 Hz), 6.92 (d, 2H, J = 8.8 Hz), 6.71 (d, 2H, J = 8.8 Hz).

(*S*)-{2-Hydroxy-1-[4-(4'-methoxy-biphenyl-4-yloxy)-phenylcarbamoyl]-1-methyl-ethyl}carbamic acid tert-butyl ester:



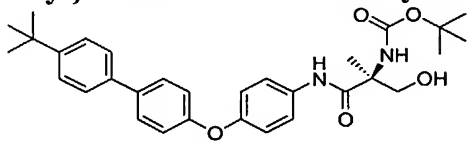
The final product was obtained as a white solid after HPLC, in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.50 (m, 6H,), 7.01-7.04 (m, 4H), 6.96 (d, 2H, J = 8.8 Hz), 4.03 (br. s, 1H), 3.85 (s, 3H) 3.57 (d, 1H, J = 11.2 Hz), 1.59 (s, 3H), 1.47 (s, 9H).

(*S*)-{1-[4-(4'-Chloro-biphenyl-4-yloxy)-phenylcarbamoyl]-2-hydroxy-1-methyl-ethyl}carbamic acid tert-butyl ester:



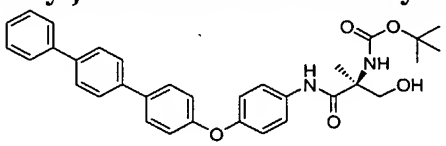
The final product was obtained as an off white solid after purification in 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.52 (m, 6H), 6.97 (d, 2H, J = 8.8 Hz), 6.90 (d, 2H, J = 8.8 Hz), 6.70 (d, 2H, J = 8.8 Hz) 4.03 (br. s, 1H), 3.57 (br.s, 1H,), 1.56 (s, 3H), 1.44 (s, 9H).

(*S*)-{1-[4-(4'-tert-Butyl-biphenyl-4-yloxy)-phenylcarbamoyl]-2-hydroxy-1-methyl-ethyl}carbamic acid tert-butyl ester:



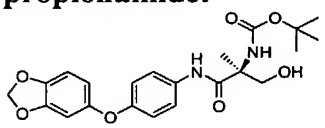
The final product was obtained as an off white solid after purification in 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.53 (m, 6H), 7.44-7.46 (m, 2H), 7.026 (dd, 4H, J = 2.4 and 8.8 Hz) 4.08 (br. s, 1H), 3.62 (br.s, 1H,), 1.59 (s, 3H), 1.47 (s, 9H), 1.36 (s, 9H).

(*S*)-{2-Hydroxy-1-methyl-1-[4-(1,1',4',1"]terphenyl-4-yloxy)-phenylcarbamoyl]-ethyl}carbamic acid tert-butyl ester:



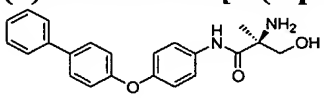
The final product was obtained as an off white solid after purification in 25% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.68 (m, 6H), 7.59 (d, 2H, J = 8.8 Hz), 7.52 (d, 2H, J = 8.8 Hz), 7.45 (t, 2H, J = 7.6 Hz), 7.36 (m, 1H), 7.05 (dd, 4H, J = 2.4 and 8.8 Hz), 3.62 (br. s, 1H), 3.40 (br.s, 1H,), 1.60 (s, 3H), 1.47 (s, 9H), 1.47 (s, 9H).

(*S*)-2-Amino-*N*-[4-(benzo[1,3]dioxol-5-yloxy)-phenyl}-3-hydroxy-2-methyl-propionamide:



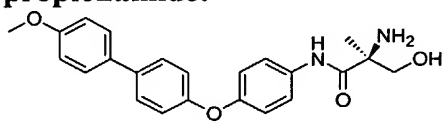
The final product was obtained as a white solid after HPLC, in 35% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, 2H, J = 8.8 Hz), 6.86 (d, 2H, J = 8.8 Hz), 6.66 (d, 1H, J = 8.4 Hz), 6.48 (d, 1H, J = 2.4 Hz), 6.38 (dd, 1H, J = 2.4 and 8.4 Hz), 5.89 (s, 2H), 4.13 (s, 1H), 3.51 (s, 1H), 1.519 (s, 3H) 1.398 (s, 9H). MS (ESI, M+H$^+$) = 331.1

(*S*)-2-Amino-*N*-[4-(biphenyl-4-yloxy)-phenyl] 3-hydroxy-2-methyl-propionamide:



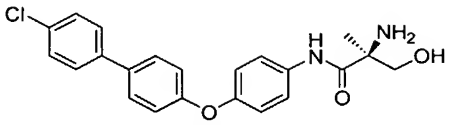
The compound was obtained as a white solid after HPLC purification. Yield: 30 %, (33mg). MS (ESI, M+H$^+$) = 362.2

(*S*)-2-Amino-3-hydroxy-*N*-[4-(4'-methoxy-biphenyl-4-yloxy)-phenyl]-2-methyl-propionamide:



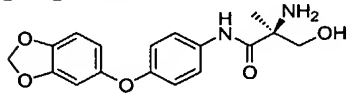
The compound was obtained as a white solid after HPLC purification. Yield: 90 %, (25mg). MS (ESI, M+H$^+$) = 393.7

(*S*)-2-Amino-3-hydroxy-*N*-[4-(4'-chloro-biphenyl-4-yloxy)-phenyl]-2-methyl-propionamide:



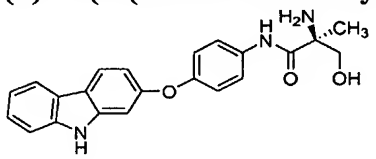
The compound was obtained as a white solid after HPLC purification. Yield: 80 %, (23mg). MS (ESI, $M+H^+$) = 396.1

(*S*)-2-Amino-*N*-[4-(benzo[1,3]dioxol-5-yloxy)phenyl]-3-hydroxy-2-methyl-propionamide:



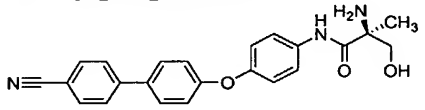
The compound was obtained as a white solid after HPLC purification. Yield: 10 %, (10mg). MS (ESI, $M+H^+$) = 331.7

(*S*)-*N*-(4-(9*H*-Carbazol-2-yloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



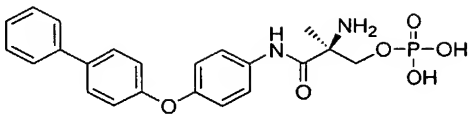
The title compound was synthesized from 2-(4-nitrophenoxy)-9H-carbazole. MS (ESI, $M+H^+$) = 376; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.17 (br s, 1H), 8.07 (br s, 1H), 7.64 (br s, 2H), 7.44 (s, 1H), 7.34 (s, 1H), 7.2-7.1 (m, 2H), 7.0 (s, 1H), 6.9 (s, 1H), 5.79 (s, 1H), 3.99 (m, 1H), 3.64 (m, 1H), 1.50 (s, 3H).

(*S*)-*N*-(4-(4-Carbonitrilephenylphenoxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



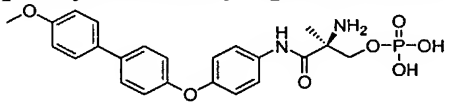
The title compound was synthesized from 4-(4-hydroxyphenyl)phenylcarbonitrile. MS (ESI, $M+H^+$) = 388; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.18 (br s, 2H), 7.92 (d, 2H), 7.86 (d, 2H), 7.75 (d, 2H), 7.67 (d, 2H), 7.12 (m, 4H), 5.79 (s, 1H), 3.99 (d, 1H), 3.64 (d, 1H), 1.50 (s, 3H).

(*S*)-Phosphoric acid mono-{2-amino-2-[4-(biphenyl-4-yloxy)-phenylcarbamoyl]-propyl} ester:



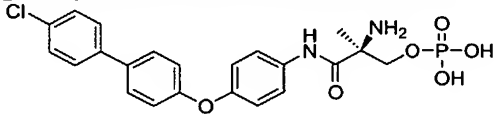
The compound was obtained as a white solid after HPLC purification. Yield: 15 %, (2.5mg). MS (ESI, $M+H^+$) = 443.4

(*S*)-Phosphoric acid mono-{2-amino-2-[4-(4'-methoxy-biphenyl-4-yloxy)-phenylcarbamoyl]-propyl} ester:



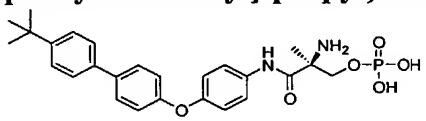
The compound was obtained as a white solid after HPLC purification. Yield: 30%, (10.0mg). MS (ESI, $M+H^+$) = 443.4

(*S*)-Phosphoric acid mono-{2-amino-2-[4-(4'-chloro-biphenyl-4-yloxy)-phenylcarbamoyl]-propyl} ester:



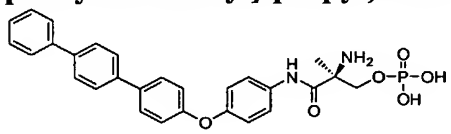
The compound was obtained as a white solid after HPLC purification. Yield: 50%, (60.0mg). MS (ESI, $M+H^+$) = 477.4

(*S*)-Phosphoric acid mono-{2-amino-2-[4-(4'-tert-butyl-biphenyl-4-yloxy)-phenylcarbamoyl]-propyl} ester:



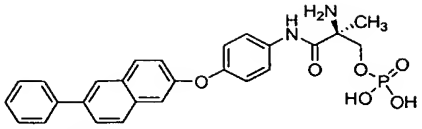
The compound was obtained as a white solid after HPLC purification. Yield: 40%, (38mg). MS (ESI, $M+H^+$) = 477.4

(*S*)-Phosphoric acid mono-{2-amino-2-[4-(1,1',4']-terphenyl-4-yloxy)-phenylcarbamoyl]-propyl} ester:



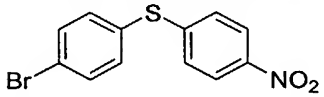
The compound was obtained as a white solid after HPLC purification. Yield: 35%, (7mg). MS (ESI, $M+H^+$) = 519.2

(*S*)-2-(4-(2-Phenylnaphthalen-6-yloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



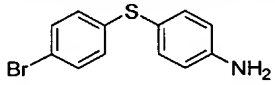
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 9.4 (bs, 2H), 8.2 (d, 1H), 8.0 (d, 1H), 7.92 (m, 2H), 7.8 (m, 2H), 7.7 (m, 2H), 7.5 (m, 2H), 7.35 (m, 2H), 7.15 (m, 2H), 4.3 (t, 1H), 4.0 (t, 1H), 1.50 (s, 3H).

4-(4-Bromo-phenylsulfanyl)-nitrobenzene:



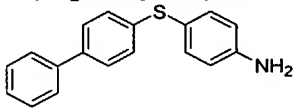
The final product was obtained as pale yellow oil after column chromatography, in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, 2H, J = 9.2 Hz), 7.58 (d, 2H, J = 8.8 Hz), 7.39 (d, 2H, J = 8.8 Hz), 7.2 (d, 2H, J = 9.2 Hz).

4-(4-Bromo-phenylsulfanyl)-phenylamine:



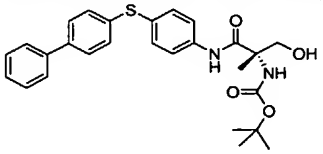
The final product was obtained as a pale yellow solid after column chromatography, in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.32 (m, 4H), 6.96 (d, 2H, J = 8.8 Hz), 6.68 (d, 2H, J = 8.4 Hz).

4-(Biphenyl-4-ylsulfanyl)-phenylamine:



The final product was obtained as a pale yellow solid after column chromatography, in 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, 2H, J = 8.4 Hz), 7.45 (d, 2H, J = 8.4 Hz), 7.40 (d, 2H, J = 7.6 Hz), 7.35 (d, 2H, J = 8.8 Hz), 7.31 (m, 1H), 7.19 (d, 2H, J = 8.4 Hz), 6.73 (d, 2H, J = 7.2 Hz).

(*S*)-(1-{4-[2-(Biphenyl-4-ylsulfanyl)-phenylcarbamoyl]-2-hydroxy-1-methyl-ethyl}-carbamic acid tert-butyl ester:



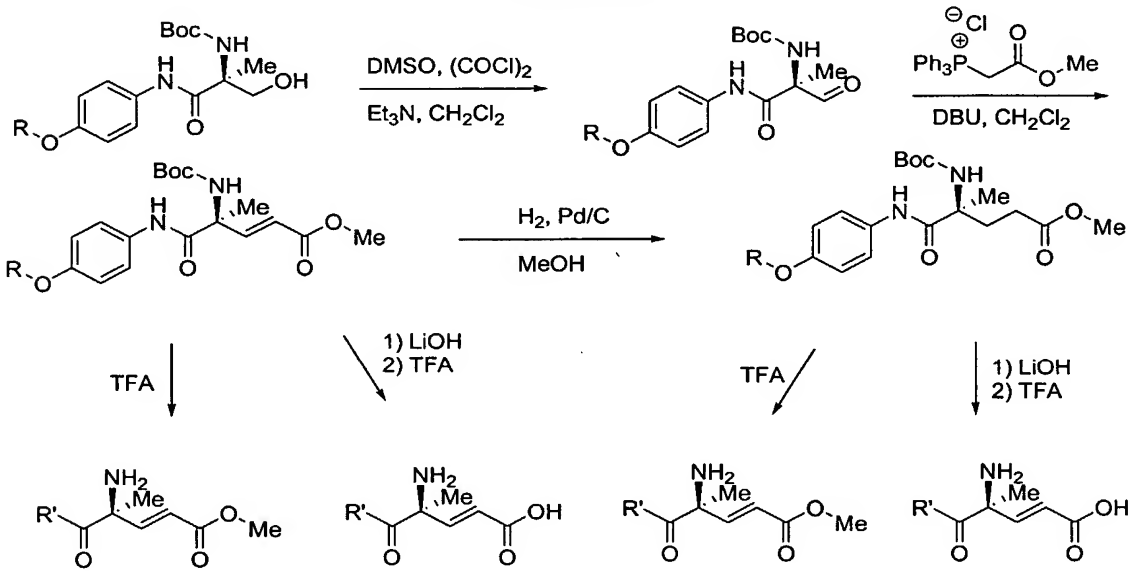
The final product was obtained as a pale yellow solid after column chromatography, in 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 2H, J = 8.4 Hz), 7.44 (m, 4H), 7.39

(d, 2H, J = 7.6 Hz), 7.35 (d, 2H, J = 8.8Hz), 7.31 (m, 1H), 7.19 (d, 2H, J = 8.4 Hz), 4.08 (br.s, 1H), 3.67 (br. s, 1H), 1.58 (s, 3H), 1.46 (s, 9H).

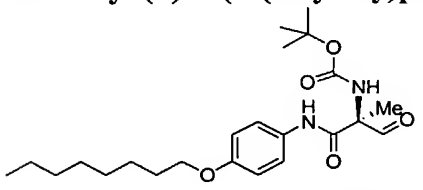
Example 10: Synthesis of α-Methyl-Glutamate Analogs

A number of α-methyl-glutamate analogs were synthesized as potential phosphate mimics using the process described in Scheme 9. Oxidation of the alcohol in α-methyl-serine protected precursor followed by a Wittig olefination provided conjugated methyl ester as the desired intermediate. The methyl ester intermediate was then either deprotected or hydrolyzed to provide the desired product or was taken through a hydrogenation before conversion to the desired product.

Scheme 9.



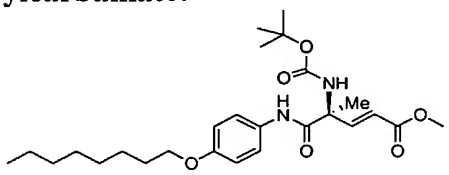
***tert*-Butyl (*S*)-1-(4-(octyloxy)phenylcarbamoyl)-1-formylethylcarbamate:**



To a solution of DMSO (0.28 mL, 3.3 equiv) in dry CH_2Cl_2 (10 mL) at -78 °C was added oxalyl chloride (0.95 mL, 1.6 equiv) drop wise then stirred for 10 minutes before addition of the desired alcohol (0.50 g, 1.0 equiv) in CH_2Cl_2 (5 mL). The mixture was stirred at -78 °C for 4 hours, then triethylamine (0.83 mL, 5 equiv) was added. The reaction was allowed to warm up to room temperature and loaded directly on a silica gel column for purification using Combi-Flash system (Hex:EtOAc). The product was obtained as a yellow solid in 60% (360 mg) yield. ^1H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 8.50 (br s, 1H), 7.37 (d, 2H, J = 7.6 Hz), 6.85 (d, 2H, J = 7.6 Hz), 5.89 (br s, 1H),

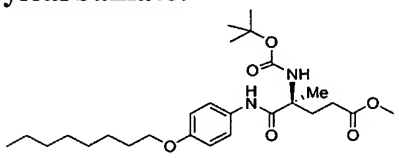
3.94 (t, 2H, J = 6.8 Hz), 1.71-1.80 (m, 2H), 1.67 (s, 3H), 1.46 (s, 9H), 1.22-1.48 (m, 10H), 0.88 (t, 3H, J = 6.8 Hz),.

tert-Butyl (_S,E_)-2-(4-(octyloxy)phenylcarbamoyl)-4-(methoxycarbonyl)but-3-en-2-ylcarbamate:



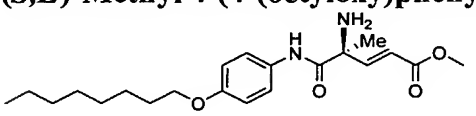
To a solution of (carbomethoxymethyl)triphenylphosphonium chloride (160 mg, 1.0 equiv) in dry CH_2Cl_2 (3 mL) at room temperature was added DBU (64 μL, 1.2 equiv) then stirred for 15 minutes before addition of the desired aldehyde (150 mg, 1.2 equiv) in CH_2Cl_2 (2 mL). The mixture was stirred at room temperature for 2 hours then directly loaded on a silica gel column for purification using Combi-Flash system (Hex:EtOAc). The product was obtained as colorless oil in 74% (125 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (br s, 1H), 7.37 (d, 2H, J = 8.6 Hz), 6.85 (d, 2H, J = 8.6 Hz), 6.04 (d, 1H, J = 16.0 Hz), 5.30 (br s, 1H), 3.92 (t, 2H, J = 6.8 Hz), 3.78 (s, 3H), 1.70-1.82 (m, 2H), 1.64 (s, 3H), 1.43 (s, 9H), 1.23-1.48 (m, 10H), 0.89 (t, 3H, J = 6.8 Hz).

tert-Butyl (_S_)-2-(4-(octyloxy)phenylcarbamoyl)-4-(methoxycarbonyl)butan-2-ylcarbamate:



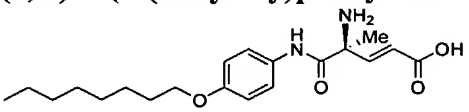
To a solution of the olefin (90 mg, 1.0 equiv) in MeOH (4 mL) was added activated Pd on carbon (9 mg in EtOAc (1 mL). The reaction was stirred under H_2 (gas) atmosphere overnight. The reaction was filtered through a layer of Celite to remove the Pd and carbon. The product was obtained as a white solid in 93% (84 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (br s, 1H), 7.39 (d, 2H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.8 Hz), 5.42 (br s, 1H), 5.30 (s, 1H), 3.92 (t, 2H, J = 6.8 Hz), 3.67 (s, 3H), 2.38-2.52 (m, 2H), 2.20-2.38 (m, 2H), 1.71-1.81 (m, 2H), 1.57 (s, 3H), 1.45 (s, 9H), 1.22-1.54 (m, 10H), 0.89 (t, 3H, J = 6.8 Hz).

(_S,E_)-Methyl 4-(4-(octyloxy)phenylcarbamoyl)-4-aminopent-2-enoate:



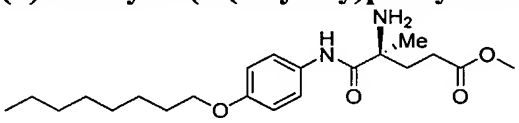
The product was obtained as colorless thick oil in 97% (14 mg) yield. MS (ESI, $M+H^+$) = 377.7; ^1H NMR (400 MHz, DMSO-d_6) δ 9.93 (br s, 1H), 8.70 (br s, 2H), 7.44 (d, 2H, J = 8.8 Hz), 7.13 (d, 1H, J = 16.0 Hz), 6.90 (d, 2H, J = 8.8 Hz), 6.22 (d, 1H, J = 16.0 Hz), 3.91 (t, 2H, J = 6.8 Hz), 3.71 (s, 3H), 1.62-1.72 (m, 2H), 1.47 (s, 3H), 1.22-1.42 (m, 10H), 0.84 (t, 3H, J = 6.8 Hz).

(*S,E*)-4-(4-(Octyloxy)phenylcarbamoyl)-4-aminopent-2-enoic acid:



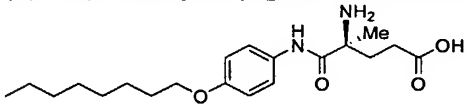
The product was obtained as a white solid in 99% (20 mg) yield. MS (ESI, $M+H^+$) = 363.7; ^1H NMR (400 MHz, DMSO-d_6) δ 9.95 (br s, 1H), 7.54 (d, 2H, J = 8.8 Hz), 7.14 (d, 1H, J = 16.0 Hz), 6.97 (d, 2H, J = 8.8 Hz), 6.15 (d, 1H, J = 16.0 Hz), 3.98 (t, 2H, J = 6.8 Hz), 1.74 (s, 3H), 1.65-1.78 (m, 2H), 1.22-1.50 (m, 10H), 0.94 (t, 3H, J = 6.8 Hz).

(*S*)-Methyl 4-(4-(octyloxy)phenylcarbamoyl)-4-aminopentanoate:



The product was obtained as colorless thick oil in 93% (13 mg) yield. MS (ESI, $M+H^+$) = 379.6; ^1H NMR (400 MHz, DMSO-d_6) δ 9.83 (br s, 1H), 8.26 (br s, 2H), 7.44 (d, 2H, J = 8.8 Hz), 6.90 (d, 2H, J = 8.8 Hz), 3.91 (t, 2H, J = 6.8 Hz), 3.56 (s, 3H), 2.10-2.40 (m, 4H), 1.62-1.72 (m, 2H), 1.41 (s, 3H), 1.20-1.42 (m, 10H), 0.84 (t, 3H, J = 6.8 Hz).

(*S*)-4-(4-(Octyloxy)phenylcarbamoyl)-4-aminopentanoic acid:



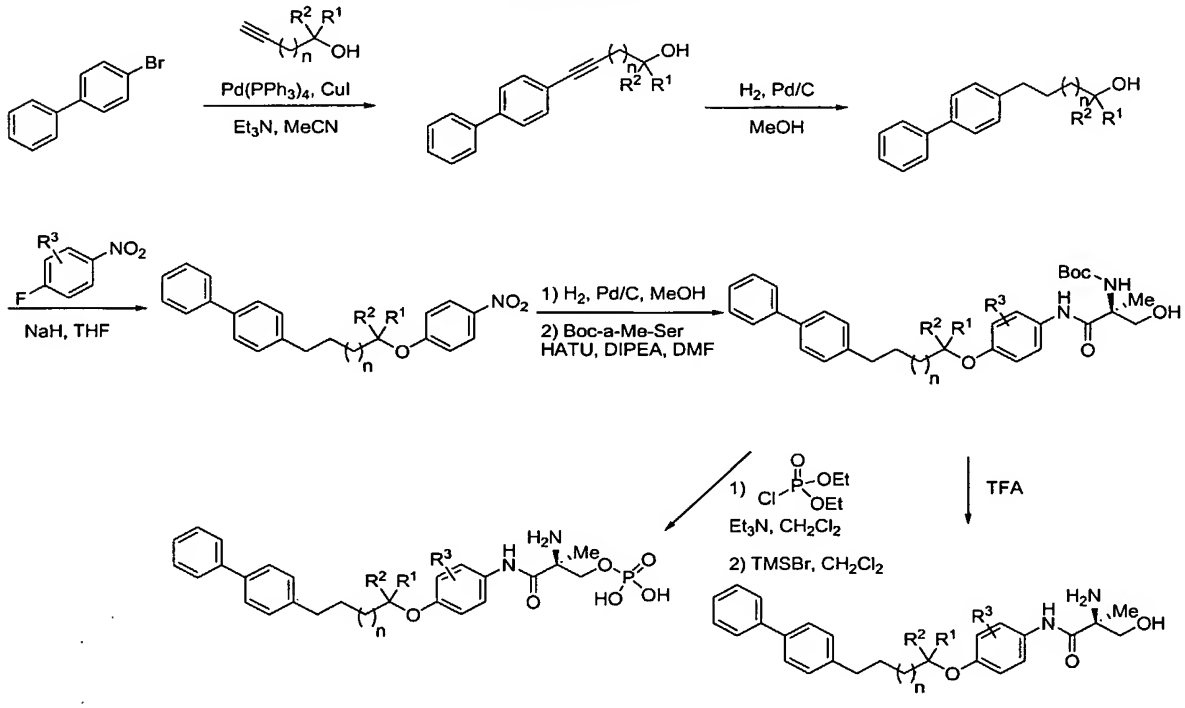
The product was obtained as a white solid in 95% (19 mg) yield. MS (ESI, $M+H^+$) = 365.8; ^1H NMR (400 MHz, DMSO-d_6) δ 9.88 (br s, 1H), 7.39 (d, 2H, J = 8.8 Hz), 6.84 ((d, 2H, J = 8.8 Hz), 3.86 (t, 2H, J = 6.8 Hz), 1.92-2.30 (m, 4H), 1.57-1.67 (m, 2H), 1.49 (s, 3H), 1.15-1.38 (m, 10H), 0.81 (t, 3H, J = 6.8 Hz).

***Linker modification*:**

A number of biphenyl-tail analogs with different linker lengths were synthesized using the process described in Scheme 10. Under Sonogashira conditions various alkynols were reacted with 4-bromobiphenyls followed by hydrogenation to afford

biphenylalkyl alcohol intermediates. Reaction of the alcohol with substituted 4-fluoro-nitrobenzene under Williamson ether synthesis conditions followed by hydrogenation and coupling with amino acid provided the desired protected alcohol which was phosphorylated or deprotected to obtain the final product.

Scheme 10



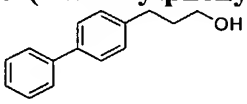
General procedure for Sonogashira cross-coupling:

To a mixture of a 4-bromobiphenyl (1.0 equiv), $Pd(PPh_3)_4$ (0.02 equiv) and CuI (0.04 equiv) in MeCN was added the alkynol (1.5 equiv) and Et_3N (1.5 equiv). The reaction mixture was stirred for 2-16 hours at reflux, then the solvent removed in vacuo. The crude product was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc) as required.

General procedure for Williamson ether synthesis:

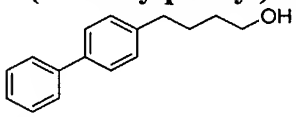
To a solution of biphenylalkyl alcohol (1.0 equiv) in dry THF under nitrogen atmosphere was added NaH (2.5 equiv) in portions. The reaction mixture was heat at 60 °C for 15 minutes, then 4-flouro-nitrobenzene (1.0 equiv) was added and the solution stirred for 1-6 hours. The reaction was allowed to cool to room temperature then quenched with water. The mixture was then diluted with EtOAc and washed with H_2O (2 x), 10% KHSO4 (1 x), and saturated NaCl (1 x). The product was either carried forward as is or it was purified by silica gel column chromatography using the Combi-Flash system (Hex:EtOAc).

3-(4-Phenylphenyl)propan-1-ol:



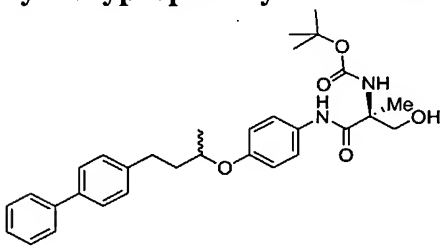
The product was obtained as a yellow solid in 57% (0.56 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.60 (m, 2H), 7.49-7.54 (m, 2H), 7.39-7.45 (m, 2H), 7.30-7.35 (m, 1H), 7.25-7.30 (m, 2H), 3.71 (t, 2H, J = 6.8 Hz), 2.76 (t, 2H, J = 6.8 Hz), 1.88-1.98 (m, 2H), 1.32 (br s, 1H).

4-(4-Phenylphenyl)butan-1-ol:



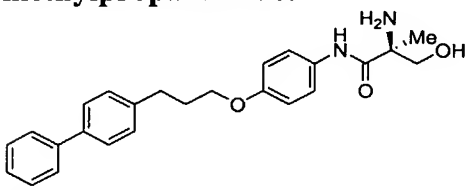
The product was obtained as a white solid in 62% (0.62 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.60 (m, 2H), 7.48-7.54 (m, 2H), 7.39-7.45 (m, 2H), 7.29-7.35 (m, 1H), 7.23-7.28 (m, 2H), 3.70 (t, 2H, J = 6.8 Hz), 2.71 (t, 2H, J = 6.8 Hz), 1.60-1.80 (m, 4H), 1.22 (br s, 1H).

***tert*-Butyl (*S*)-2-(4-(4-(4-phenylphenyl)butan-2-yloxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate:**



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (br s, 1H), 8.11 (br s, 2H), 7.60-7.64 (m, 2H), 7.58 (d, 2H, J = 8.8 Hz), 7.51 (d, 2H, J = 8.6 Hz), 7.37-7.48 (m, 4H), 7.32 (t, 1H, J = 8.6 Hz), 6.84 (d, 2H, J = 8.8 Hz), 5.61 (br s, 1H), 4.30-4.38 (m, 1H), 4.10 (br s, 1H), 3.56 (br s, 1H), 3.28 (br s, 1H), 2.70-2.90 (m, 2H), 2.01-2.14 (m, 1H), 1.84-1.96 (m, 1H), 1.58 (s, 3H), 1.46 (s, 9H), 1.31 (d, 3H, J = 7.0 Hz).

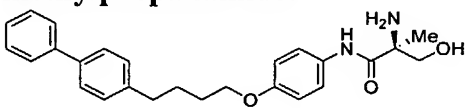
(*S*)-*N*-(4-(3-(4-Phenylphenyl)propoxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



MS (ESI, M+H$^+$) = 405.5; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (br s, 1H), 8.11 (br s, 2H), 7.60-7.64 (m, 2H), 7.57 (d, 2H, J = 8.8 Hz), 7.47 (d, 2H, J = 8.8 Hz), 7.43 (t, 2H, J

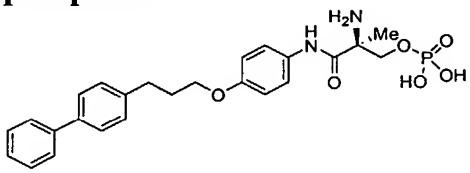
= 8.6 Hz), 7.28-7.35 (m, 2H), 6.92 (d, 2H, J = 8.8 Hz), 3.95 (t, 2H, J = 6.8 Hz), 3.93 (dd, 1H, J = 12.0 Hz, J = 4.8 Hz), 3.61 (dd, 1H, J = 12.0 Hz, J = 5.0 Hz), 2.76 (t, 2H, J = 6.8 Hz), 1.98-2.08 (m, 2H), 1.47 (br s, 1H).

(*S*)-*N*-(4-(4-(4-Phenylphenyl)butoxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



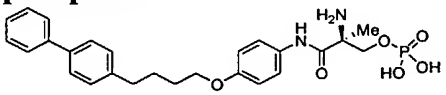
MS (ESI, M+H$^+$) = 419.5; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.73 (br s, 1H), 8.11 (br s, 2H), 7.60-7.64 (m, 2H), 7.56 (d, 2H, J = 8.8 Hz), 7.40-7.49 (m, 4H), 7.27-7.35 (m, 3H), 6.91 (d, 2H, J = 8.8 Hz), 3.95 (t, 2H, J = 6.8 Hz), 3.94 (dd, 1H, J = 12.0 Hz, J = 4.8 Hz), 3.60 (dd, 1H, J = 12.0 Hz, J = 5.2 Hz), 2.62-2.70 (m, 2H), 1.68-1.77 (m, 4H), 1.46 (br s, 1H).

(*S*)-2-(4-(3-(4-Phenylphenyl)propoxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



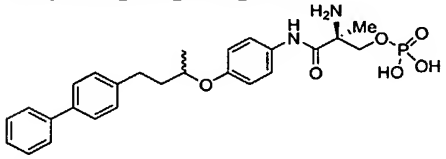
The product was obtained as a white solid in 25% (7.0 mg) yield over two steps. MS (ESI, M+H$^+$) = 485.6.

(*S*)-2-(4-(4-(4-Phenylphenyl)butoxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



The product was obtained as a white solid in 43% (12.0 mg) yield over two steps. MS (ESI, M+H$^+$) = 499.6.

(*S*)-2-(4-(4-(4-Phenylphenyl)butan-2-yloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:

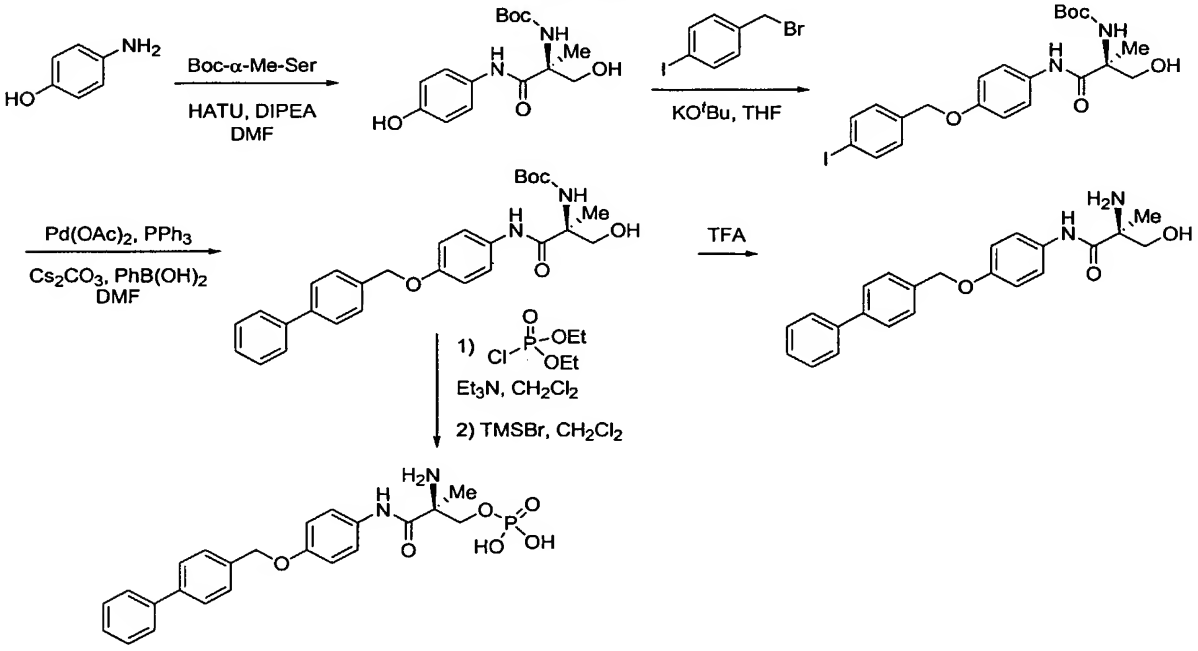


The product was obtained as a white solid in 30% (9.0 mg) yield over two steps. MS (ESI, M+H$^+$) = 499.6.

One carbon length Linker:

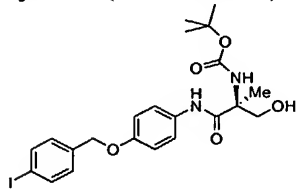
One carbon-ether length biphenyl-tail analogs were synthesized using the process described in Scheme 11. After *N*-acylation of 4-aminophenol, benzyl ether synthesis was achieved under mild alkylation condition. The biphenyl tail was synthesized using mild Suzuki cross-coupling using phenylboronic acid. The obtained protected alcohol was then further modified to phosphorylate or deprotected to produce the desired final product.

Scheme 11



***tert*-Butyl (*S*)-2-(4-(4-iodobenzyloxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate:**

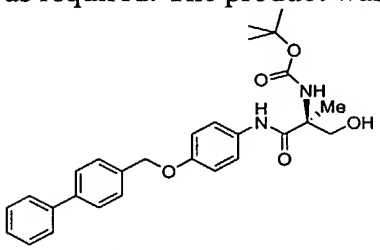
To a solution of *N*-acylated 4-aminophenol (300 mg, 1.0 equiv) in dry THF (6 mL) at room temperature was added a 1.0 M solution of KO*t*Bu in THF (0.97 mL, 1.0 equiv) and stirred for 10 minutes before addition of 4-iodobenyl bromide (290 mg, 1.0 equiv). The solution was stirred for 3 hoursand subsequently the solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography using Combi-Flash system (Hex:EtOAc). The product was obtained as a white foam in 40% (203 mg) yield.



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (br s, 1H), 7.70 (d, 2H, J = 8.6 Hz), 7.41 (d, 2H, J = 8.6 Hz), 7.18 (d, 2H, J = 8.6 Hz), 6.90 (d, 2H, J = 8.6 Hz), 5.60 (br s, 1H), 4.99 (s, 2H), 4.08 (br s, 1H), 3.55 (br s, 1H), 3.22 (br s, 1H), 1.58 (s, 3H), 1.46 (s, 9H).

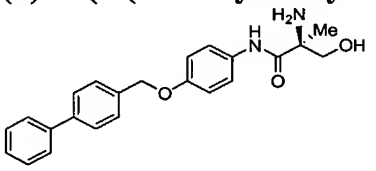
***tert*-Butyl (*S*)-2-(4-(4-phenylbenzyloxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate:**

To a mixture of a substituted aryl iodide (120 mg, 1.0 equiv), phenyl boronic acid (35 mg, 1.2 equiv), $Pd(OAc)_2$ (5 mg, 0.1 equiv), triphenylphosphine (12 mg, 0.2 equiv), and cesium carbonate (74 mg, 1.0 equiv) was added DMF (4 mL). The mixture was heated at 50 °C for an hour. The reaction was then diluted with EtOAc (20 mL) and washed with H_2O (2 x 25 mL) then the solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography using Combi-Flash system (Hex:EtOAc) as required. The product was obtained as a white solid in 79% (85 mg) yield.



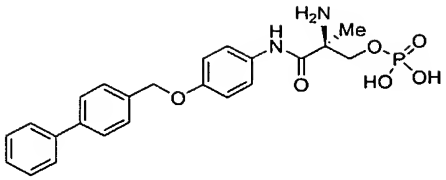
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (br s, 1H), 7.57-7.63 (m, 4H), 7.40-7.52 (m, 6H), 7.32-7.38 (m, 1H), 6.98 (d, 2H, J = 8.6 Hz), 5.61 (br s, 1H), 5.09 (s, 2H), 4.09 (br s, 1H), 3.56 (br s, 1H), 3.27 (br s, 1H), 1.58 (s, 3H), 1.47 (s, 9H).

(*S*)-*N*-(4-(4-Phenylbenzyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



The product was obtained as a white solid in 45% (9.0 mg) yield. MS (ESI, $M+H^+$) = 377.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (br s, 1H), 8.12 (br s, 1H), 7.63-7.69 (m, 4H), 7.42-7.53 (m, 6H), 7.32-7.38 (m, 1H), 7.02 (d, 2H, J = 8.6 Hz), 5.74 (t, 1H, J = 5.1 Hz), 5.13 (s, 2H), 3.94 (dd, 1H, J = 11.8 Hz, J = 4.7 Hz), 3.61 (dd, 1H, J = 11.8 Hz, J = 4.7 Hz), 1.46 (s, 3H).

(*S*)-2-(4-(4-Phenylbenzyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:

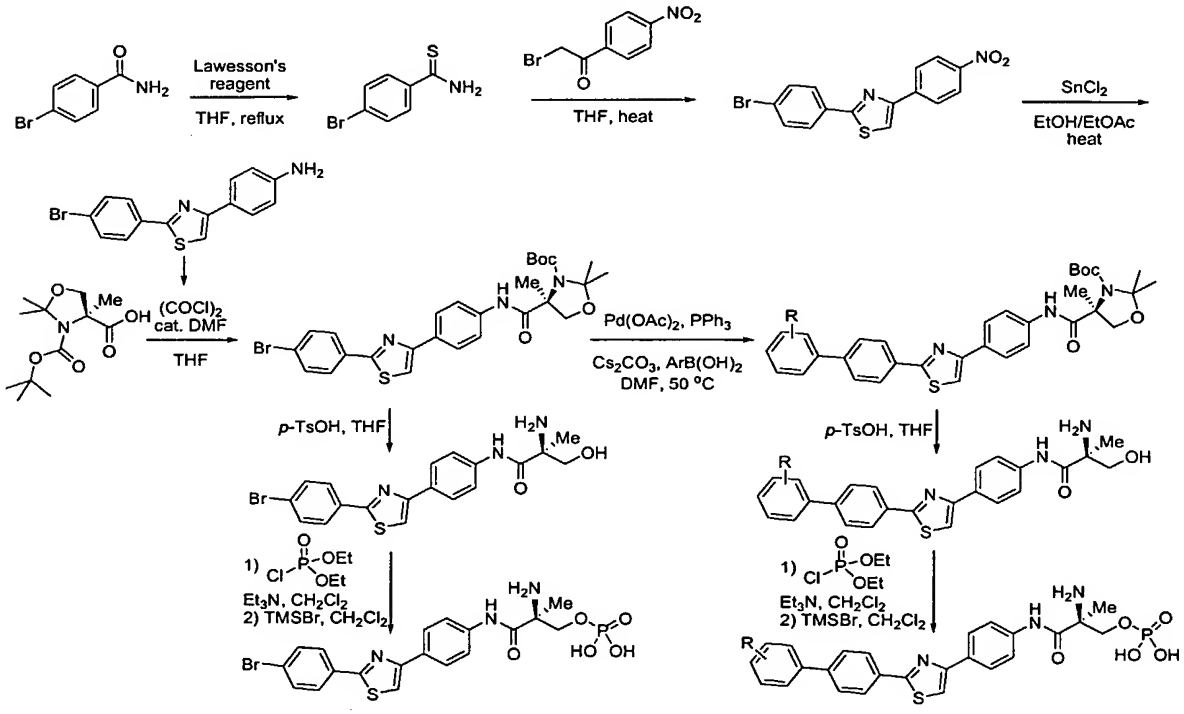


The product was obtained as a white solid in 36% (18.0 mg) yield over two steps. MS (ESI, $M+H^+$) = 457.1.

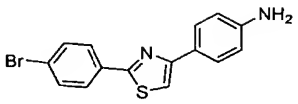
Thiazole linker:

The thiazole-biphenyl analogs were synthesized using the process described in Scheme 12. Substituted benzamide was converted to thiobenzamide using Lawesson's reagent. Reaction of thioamide with bromoketone afforded the thiazole intermediate. Reduction of the nitro group followed by acylation provided an orthogonally protected intermediate, which was further modified by a mild Suzuki cross-coupling process using aryl boronic acid. The protecting Boc and the oxazolidine groups were removed using *p*-TsOH and the product was then phosphorylated to obtain the final phosphate product.

Scheme 12



4-(2-(4-Bromophenyl)thiazol-4-yl)benzenamine:



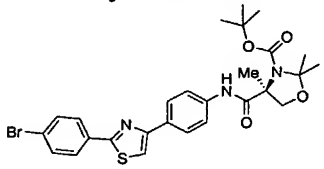
To a mixture of Lawesson's reagent (6.07 g, 1.5 equiv) and 4-bromobenzamide (2.00 g, 1.0 equiv) was added dry THF (20 mL). The reaction mixture was refluxed overnight under nitrogen atmosphere. The reaction was allowed to cool to room temperature, then diluted with EtOAc (50 mL) and washed with 5% $NaHCO_3$ (2 x 50 mL) and saturated NaCl (1 x 25 mL). The organic layer was dried over anhydrous $MgSO_4$ then the solvent removed *in vacuo*. The crude product was purified by silica gel column chromatography using Combi-Flash system (Hex:EtOAc). The product was obtained as white solid in 99% (2.16 g) yield.

To a mixture of 4-bromothiobenzamide (2.16 g, 1.0 equiv) and 4-nitro-bromoacetophenone (2.43 g, 1.0 equiv) was added dry THF (20 mL) and heated at 60 °C for 3 hours. The solvent was removed *in vacuo* and the crude product was purified by silica gel column chromatography using Combi-Flash system (Hex:EtOAc). The product was obtained as yellow solid in 84% (3.00 g) yield.

To a mixture of the nitro intermediate (1.10 g, 1.0 equiv) and $SnCl_2$ (3.02 g, 5.0 equiv) was added EtOH (30 mL) then heated at 80 °C for 3 hours. The reaction mixture was diluted with H_2O (50 mL) then basified to pH 10 using saturated NaOH solution. The reaction mixture was then extracted with EtOAc (2 x 100 mL). The organic layers were combined and removed *in vacuo*. The crude product was purified by silica gel column chromatography using Combi-Flash system (Hex:EtOAc). The product was obtained as yellow solid in 63% (0.63 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 2H, J = 8.6 Hz), 7.79 (d, 2H, J = 8.6 Hz), 7.58 (d, 2H, J = 8.6 Hz), 7.26 (d, 1H, J = 0.8 Hz), 6.75 (d, 2H, J = 8.6 Hz), 3.80 (br s, 2H).

(*S*)-*tert*-Butyl 4-(4-(2-(4-bromophenyl)thiazol-4-yl)phenylcarbamoyl)-2,2,4-trimethyloxazolidine-3-carboxylate:

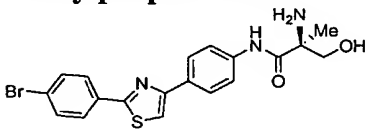


To a solution of (*S*)-3-(*tert*-butoxycarbonyl)-2,2,4-trimethyloxazolidine-4-carboxylic acid (100 mg, 1.0 equiv) in dry THF (5 mL) was added a 2.0 M solution of oxalyl chloride in CH_2Cl_2 (0.23 mL, 1.2 equiv) and catalytic amount of DMF (2 drops). The reaction was allowed to stir at room temperature for 30 minutes. To the reaction mixture was then added the desired aniline (solid or solution in THF, 128 mg, 1.0 equiv). The reaction was allowed to stir overnight. The solvent removed *in vacuo* and

the crude product was purified by silica gel column chromatography using Combi-Flash system (Hex:EtOAc). The product was obtained as a white solid in 74% (164 mg) yield.

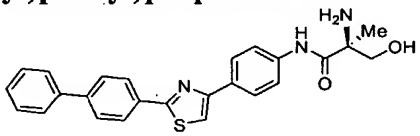
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.97 (m, 4H), 7.56-7.63 (m, 4H), 7.43 (s, 1H), 3.90 (br s, 2H), 1.70 (br s, 6H), 1.60 (br s, 3H), 1.50 (br s, 9H).

(*S*)-2-Amino-*N*-(4-(2-(4-bromophenyl)thiazol-4-yl)phenyl)-3-hydroxy-2-methylpropanamide:



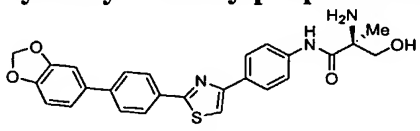
The product was obtained as a white solid in 75% (20.0 mg) yield. MS (ESI, M+H$^+$) = 432.6 and 434.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (br s, 1H), 8.18 (br s, 2H), 8.14 (s, 1H), 8.04 (d, 2H, J = 8.6 Hz), 7.96 (d, 2H, J = 8.6 Hz), 7.70-7.76 (m, 4H), 5.60 (br s, 1H), 4.00 (br d, 1H), 3.65 (br d, 1H), 1.50 (s, 3H).

(*S*)-2-Amino-3-hydroxy-2-methyl-*N*-(4-(2-(4-phenylphenyl)thiazol-4-yl)phenyl)propanamide:



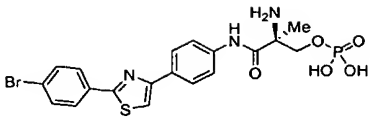
The product was obtained as a white solid in 58% (15.0 mg) yield over two steps. MS (ESI, M+H$^+$) = 430.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (br s, 1H), 8.18 (br s, 2H), 8.04-8.14 (m, 5H), 7.84 (d, 2H, J = 8.6 Hz), 7.72-7.78 (m, 4H), 7.50 (t, 2H, J = 8.6 Hz), 7.37-7.47 (m, 2H), 5.80 (br s, 1H), 4.01 (br d, 1H), 3.65 (br d, 1H), 1.51 (s, 3H).

(*S*)-2-Amino-*N*-(4-(2-(4-(benzo[*d*][1,3]dioxol-6-yl)phenyl)thiazol-4-yl)phenyl)-3-hydroxy-2-methylpropanamide:



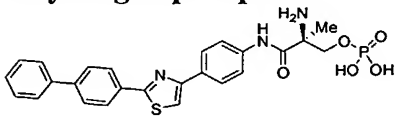
The product was obtained as a white solid in 42% (15.0 mg) yield over two steps. MS (ESI, M+H$^+$) = 474.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (br s, 1H), 8.25 (br s, 2H), 7.98-8.11 (m, 5H), 7.76-7.82 (m, 4H), 7.36 (d, 1H, J = 1.6 Hz), 7.26 (dd, 1H, J = 8.2 Hz, J = 2.0 Hz), 7.04 (d, 1H, J = 8.2 Hz), 6.09 (s, 2H), 5.05 (br s, 1H), 3.78 (br d, 1H), 3.30 (br d, 1H), 1.20 (s, 3H).

(*S*)-2-(4-(2-(4-Bromophenyl)thiazol-4-yl)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



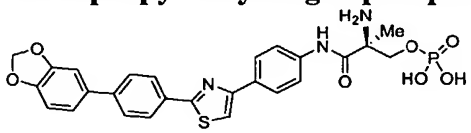
The product was obtained as a white solid in 83% (5.0 mg) yield over two steps. MS (ESI, $M+H^+$) = 512.6 and 514.3.

(*S*)-2-(4-(2-(4-Phenylphenyl)thiazol-4-yl)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



The product was obtained as a white solid in 65% (3.0 mg) yield over two steps. MS (ESI, $M+H^+$) = 510.2.

(*S*)-2-(4-(2-(4-(Benzo[*d*][1,3]dioxol-6-yl)phenyl)thiazol-4-yl)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:

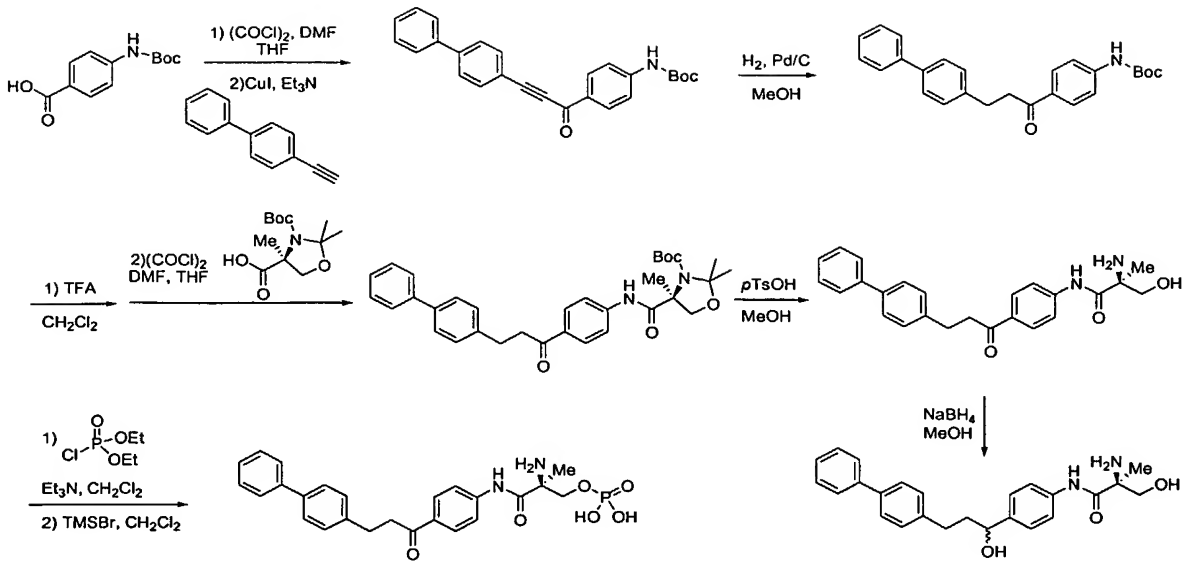


The product was obtained as a white solid in 45% (3.0 mg) yield over two steps. MS (ESI, $M+H^+$) = 554.1.

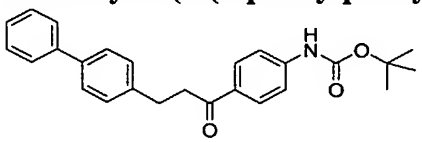
Acetophenone-based linker:

Synthesis of the acetophenone-based linker was achieved using the process described in Scheme 13. Reaction of protected 4-aminobenzoyl chloride with 4-ethynylbiphenyl followed by hydrogenation of the alkyne provided the Boc-protected 4-aminoacetophenone. Acylation of the amino group after removal of the Boc protecting group afforded an orthogonally protected oxazolidine intermediate, which could be removed using *p*-TsOH. The free alcohol could then be rapidly converted into the final phosphate product.

Scheme 13.

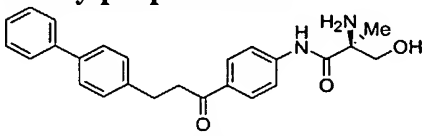


***tert*-Butyl 4-(3-(4-phenylphenyl)propanoyl)phenylcarbamate:**



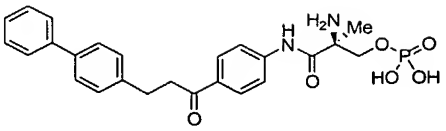
The product was obtained as a yellow solid in 25% (185 mg) yield over three steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 2H, J = 8.6 Hz), 7.50-7.60 (m, 4H), 7.40-7.46 (m, 4H), 7.30-7.36 (m, 3H), 6.66 (br s, 1H), 3.29 (t, 2H, J = 7.0 Hz), 3.10 (t, 2H, J = 7.0 Hz), 1.54 (s, 9H).

(*S*)-*N*-(4-(3-(4-Phenylphenyl)propanoyl)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



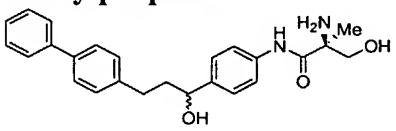
The product was obtained as a white solid in 66% (111 mg) yield over four steps. MS (ESI, M+H$^+$) = 403.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, 2H, J = 8.6 Hz), 7.80 (d, 2H, J = 8.6 Hz), 7.52-7.63 (m, 4H), 7.43 (t, 2H, J = 8.6 Hz), 7.29-7.38 (m, 3H), 4.99 (br t, 1H, J = 5.1 Hz), 3.72 (dd, 1H, J = 10.2 Hz, J = 5.2 Hz), 3.35 (t, 2H, J = 6.8 Hz), 3.20 (dd, 1H, J = 10.2 Hz, J = 5.2 Hz), 2.96 (t, 2H, J = 6.8 Hz), 1.15 (s, 3H).

(*S*)-2-(4-(3-(4-Phenylphenyl)propanoyl)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



The product was obtained as a white solid in 62% (5.0 mg) yield over two steps. MS (ESI, $M+H^+$) = 483.5.

(*S*)-2-Amino-3-hydroxy-*N*-(4-(1-hydroxy-3-(4-phenylphenyl)propyl)phenyl)-2-methylpropanamide:

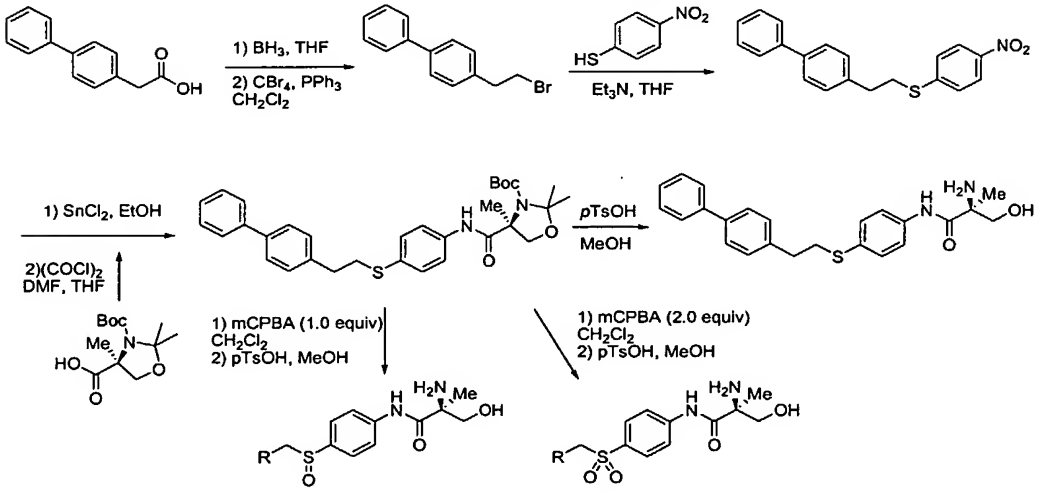


The product was obtained as a white solid in 80% (5.0 mg) yield. MS (ESI, $M+H^+$) = 405.2.

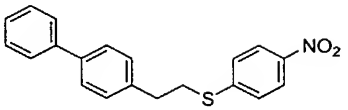
Thioether Linker:

Synthesis of the thioether, sulfoxide and sulfone linkers was achieved using the process described in Scheme 14. Reduction of biphenyl acetic acid to alcohol followed by conversion of the alcohol to bromo leaving group allowed conversion of the functional group to a thioether. The nitro group was then reduced and acylated to afford oxazolidine intermediate. The thioether could then be further functionalized before deprotection of the Boc and oxazolidine protecting groups. The free alcohol was then converted into the desired final phosphate product.

Scheme 14

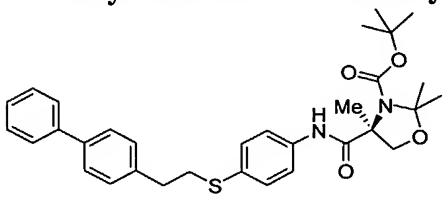


4-(2-(4-Nitrophenylthio)ethyl)biphenyl:



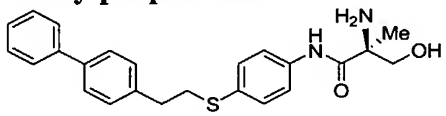
The product was obtained as a yellow solid in 73% (0.72 g) yield over three steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 2H, J = 8.6 Hz), 7.53-7.62 (m, 6H), 7.44 (t, 2H, J = 8.6 Hz), 7.28-7.38 (m, 3H), 3.32 (t, 2H, J = 7.4 Hz), 3.06 (t, 2H, J = 7.4 Hz).

(*S*)-*tert*-Butyl 4-(4-(4-phenylphenethylthio)phenylcarbamoyl)-2,2,4-trimethyloxazolidine-3-carboxylate:



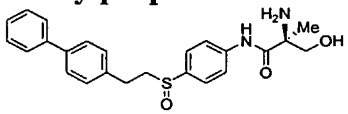
The product was obtained as a white solid in 42% (160 mg) yield over three steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.52 (m, 2H), 7.45 (d, 2H, J = 8.6 Hz), 7.41 (d, 2H, J = 8.8 Hz), 7.36 (t, 2H, J = 8.6 Hz), 7.22-7.32 (m, 3H), 7.29-7.38 (m, 3H), 7.12 (d, 2H, J = 8.8 Hz), 3.70 (br s, 2H), 3.08 (t, 2H, J = 7.0 Hz), 2.86 (d, 2H, J = 7.0 Hz), 2.96 (t, 2H, J = 6.8 Hz), 1.62 (s, 6H), 1.48 (s, 3H), 1.43 (br s, 9H).

(*S*)-*N*-(4-(4-Phenylphenethylthio)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



The product was obtained as a white solid in 42% (160 mg) yield over three steps. MS (ESI, M+H$^+$) = 407.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (br s, 1H), 8.16 (br s, 2H), 7.54-7.64 (m, 6H), 7.44 (d, 2H, J = 8.6 Hz), 7.28-7.40 (m, 5H), 5.76 (br s, 1H), 3.99 (br dd, 2H), 3.63 (br dd, 1H), 3.22 (t, 2H, J = 7.0 Hz), 2.87 (t, 2H, J = 6.8 Hz), 1.49 (s, 3H).

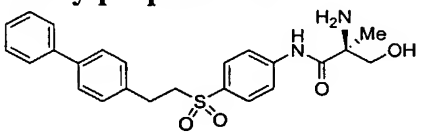
(2*S*)-*N*-(4-(4-Phenylphenethylsulfinyl)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



The product was obtained as a white solid in 90% (40 mg) yield over two steps. MS (ESI, M+H$^+$) = 423.7; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (br s, 1H), 8.23 (br s, 2H), 7.88 (d, 2H, J = 8.6 Hz), 7.68 (d, 2H, J = 8.6 Hz), 7.61 (dd, 2H, J = 8.6 Hz, J = 1.6 Hz), 7.56 (d, 2H, J = 8.6 Hz), 7.43 (t, 2H, J = 8.6 Hz), 7.27-7.36 (m, 3H), 5.78 (br s,

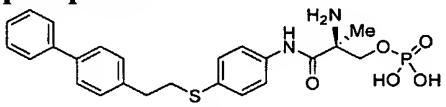
1H), 4.05 (br d, 2H), 3.53 (br d, 1H), 3.20-3.43 (m, 1H), 2.90-3.10 (m, 2H), 2.67-2.78 (m, 1H0, 1.48 (s, 3H).

(*S*)-*N*-(4-(4-Phenylphenethylsulfonyl)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



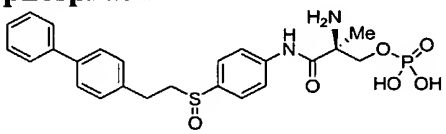
The product was obtained as a white solid in 91% (52 mg) yield over two steps. MS (ESI, $M+H^+$) = 439.4; ^1H NMR (400 MHz, DMSO-d_6) δ 10.41 (br s, 1H), 8.25 (br s, 2H), 7.86-7.99 (m, 4H), 7.59 (d, 2H, J = 8.6 Hz), 7.52 (d, 2H, J = 8.6 Hz), 7.42 (t, 2H, J = 8.6 Hz), 7.32 (tt, 1H, J = 8.4 Hz, J = 1.2 Hz), 7.27 (d, 2H, J = 8.6 Hz), 5.80 (br t, 1H), 4.06 (dd, 1H, J = 11.6 Hz, J = 4.7 Hz), 3.58-3.69 (m, 3H), 2.85-2.93 (m, 2H), 1.52 (s, 3H).

(*S*)-2-(4-(4-Phenylphenethylthio)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



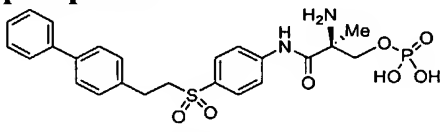
The product was obtained as a white solid in 65% (6.0 mg) yield over two steps. MS (ESI, $M+H^+$) = 487.3.

(*S*)-2-(4-(4-Phenylphenethylsulfinyl)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



The product was obtained as a white solid in 45% (1.5 mg) yield over two steps. MS (ESI, $M+H^+$) = 503.1.

(*S*)-2-(4-(4-Phenylphenethylsulfonyl)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:

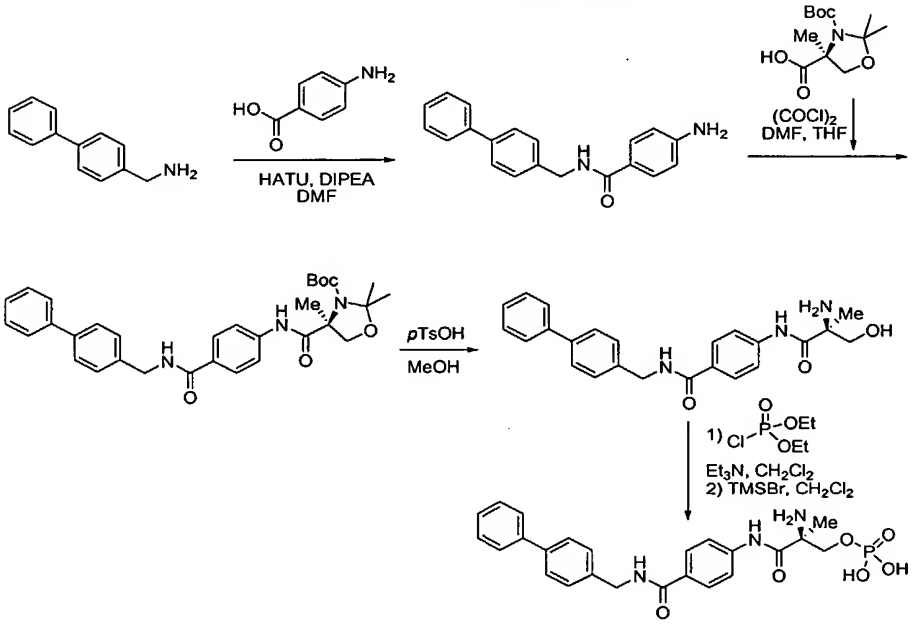


The product was obtained as a white solid in 65% (15.0 mg) yield over two steps. MS (ESI, $M+H^+$) = 519.7.

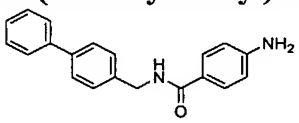
Benzamide linker:

The benzamide linker based compounds were synthesized as described in Scheme 15. Acylation of 4-phenylbenzylamine followed by a one-pot, two step acylation of the aniline intermediate afforded orthogonally protected oxazolidine intermediate. The oxazolidine intermediate was then converted into free alcohol and its phosphate respectively.

Scheme 15

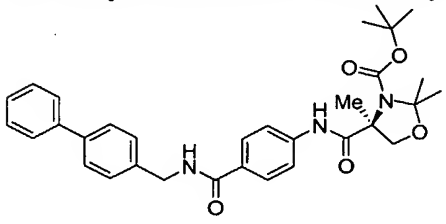


N-(4-Phenylbenzyl)-4-aminobenzamide:



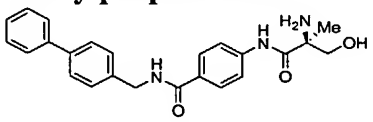
The product was obtained as a yellow solid in 60% (0.49 g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, 2H, J = 8.6 Hz), 7.55-7.60 (m, 4H), 7.40-7.47 (m, 4H), 7.35 (tt, 1H, J = 8.6 Hz, J = 1.2 Hz), 6.66 (d, 2H, J = 8.6 Hz), 6.25 (br t, 1H), 4.67 (d, 2H, J = 5.9 Hz), 3.95 (br s, 2H).

(*S*)-*tert*-Butyl 4-(4-(4-phenylbenzylcarbamoyl)phenylcarbamoyl)-2,2,4-trimethyloxazolidine-3-carboxylate:



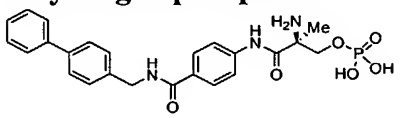
The product was obtained as a white solid in 43% (105 mg) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 2H, J = 8.8 Hz), 7.55-7.63 (m, 6H), 7.41-7.47 (m, 4H), 7.35 (tt, 1H, J = 8.6 Hz, J = 1.2 Hz), 6.37 (br t, 1H), 4.69 (d, 2H, J = 5.5 Hz), 3.78 (br s, 2H), 1.69 (s, 6H), 1.59 (s, 3H), 1.48 (br s, 9H).

(*S*)-*N*-(4-(*N'*-(4-Phenylbenzyl)formamido)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



The product was obtained as a white solid in 61% (35 mg) yield. MS (ESI, M+H$^+$) = 404.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (br 1, 1H, J = 5.8 Hz), 7.87 (d, 2H, J = 8.6 Hz), 7.77 (d, 2H, J = 8.6 Hz), 7.60-7.66 (m, 4H), 7.32-7.48 (m, 5H), 7.10 (br d, 1H), 5.02 (br t, 1H), 4.50 (d, 2H, J = 5.8 Hz), 3.75 (dd, 1H, J = 10.5 Hz, J = 5.5 Hz), 3.22 (dd, 1H, J = 10.5 Hz, J = 5.1 Hz), 1.17 (s, 3H).

(*S*)-2-(4-(*N'*-(4-Phenylbenzyl)formamido)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:

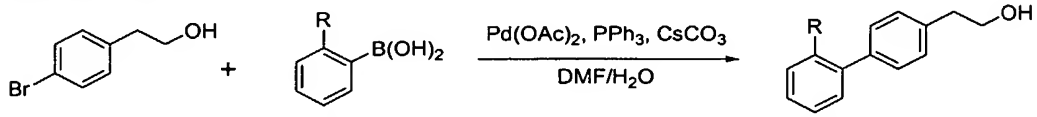


The product was obtained as a white solid in 30% (7.0 mg) yield over two steps. MS (ESI, M+H$^+$) = 484.7.

Biphenyl ethanol linker:

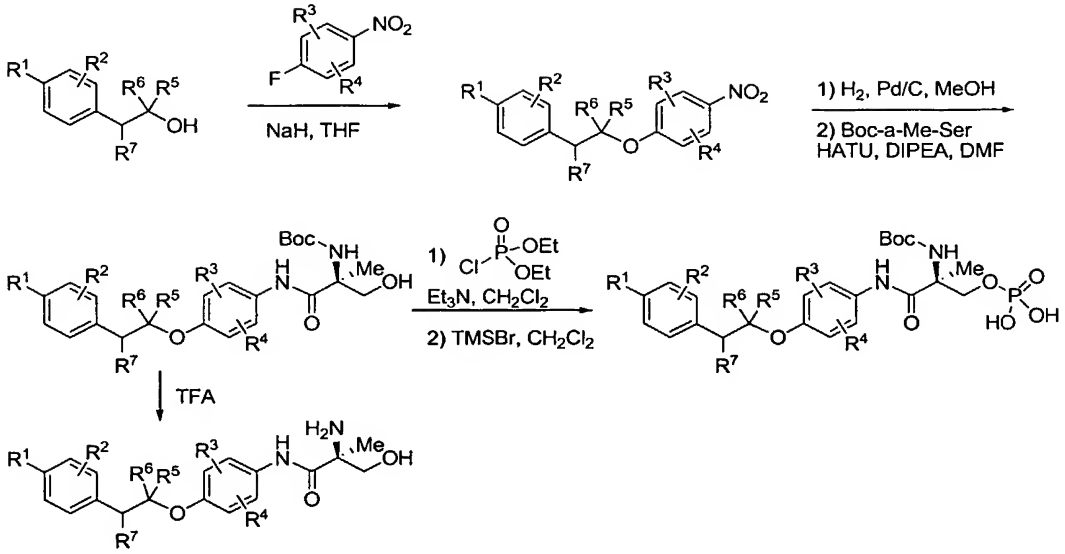
A number of substituted biphenyl ethanols were synthesized using a Suzuki cross-coupling protocol a described in Scheme 16.

Scheme 16.



Reaction of the substituted biphenyl ethanol with substituted 4-fluoro-nitrobenzene under Williamson ether synthesis (scheme 17) conditions followed by hydrogenation and coupling with amino acid provided the Boc protected amino-alcohol which was further phosphorylated or deprotected to obtain the desired final product.

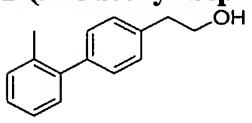
Scheme 17.



General procedure for synthesis of substituted biaryl ethanol:

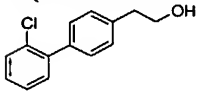
To a DMF solution of the 4-(haloaryloxy)-aniline (1.0 equiv) and substituted aryl boronic acid in a microwave tube, was added $Pd(OAc)_2$ (0.1 equiv), triphenyl phosphine (0.2 equiv), cesium carbonate (1.0-1.5 equiv) and TBAC (0.1 equiv). The reaction was then sealed and heated at 50-70 °C for 3-18 hours using an oil bath. The reaction mixture was diluted with EtOAc (25 mL), washed with water (2 x 10 mL) and then brine (1 x 10 mL). The organic layer was then dried over $MgSO_4$, and then solvent removed under reduced pressure. The crude product was purified using the Combi-Flash silica gel column chromatography, using a Hexane/EtOAc gradient.

2-(2'-Methyl-biphenyl-4-yl)-ethanol:



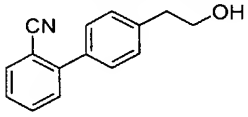
The final product was obtained as a white solid after column chromatography, in 85% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 4H), 7.26 (s, 4H), 3.93 (t, 2H, J = 6.4 Hz), 2.93 (t, 2H, J = 6.4 Hz), 2.28 (s, 3H).

2-(2'-Chloro-biphenyl-4-yl)-ethanol



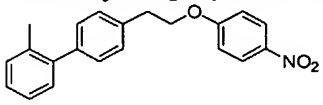
The final product was obtained as a white solid after column chromatography, in 85% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.48 (m, 1H), 7.405 (d, 2H, J = 8.0 Hz), 7.28–7.33 (m, 4H), 3.93 (t, 2H, J = 6.4 Hz), 2.94 (t, 2H, J = 6.4 Hz).

2-(2-Cyano-biphenyl-4-yl)-ethanol:



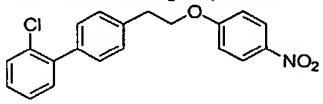
The final product was obtained as a white solid after column chromatography, in 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, 1H, J = 8.0 and 1.2), 7.64 (m, 1H), 7.49–7.53 (m, 3H), 7.43 (m, 1H), 7.36 (d, 2H, J = 8.0 Hz), 3.93 (t, 2H, J = 6.8 Hz), 2.95 (t, 2H, J = 6.4 Hz).

2-Methyl-4'[2-(4-nitro-phenoxy)-ethyl]-biphenyl:



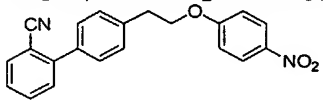
The final product was obtained as a yellow solid after column chromatography, in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, 2H, J = 9.2 Hz), 7.2-7.316 (m, 8H), 6.97 (d, 2H, J = 8.8 Hz), 4.32 (t, 2H, J = 7.2 Hz), 3.19 (t, 2H, J = 6.8 Hz), 2.27 (s, 3H).

2-Chloro-4'[2-(4-nitro-phenoxy)-ethyl]-biphenyl:



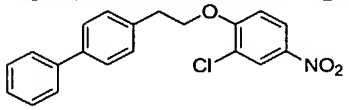
The final product was obtained as a yellow solid after column chromatography, in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, 2H, J = 9.2 Hz), 7.41-7.48 (m, 3H), 7.27-7.36 (m, 4H), 7.24 (s, 1H), 6.97 (d, 2H, J = 9.2 Hz), 4.32 (t, 2H, J = 6.8 Hz), 3.20 (t, 2H, J = 6.8 Hz).

4'-[2-(4-Nitro-phenoxy)-ethyl]-biphenyl-2-carbonitrile:



The final product was obtained as an off white solid after column chromatography, in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, 2H, J = 9.2 Hz), 7.76 (dd, 1H, J = 8.0 and 1.2), 7.66-7.62 (m, 1H), 7.54-7.49 (m, 3H), 7.40-7.46 (m, 3H), 6.96 (d, 2H, J = 9.2 Hz), 4.31 (t, 2H, J = 6.8 Hz), 3.21 (t, 2H, J = 6.8 Hz).

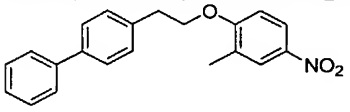
4-[2-(2-Chloro-4-nitro-phenoxy)-ethyl]biphenyl:



The final product was obtained as a yellow solid after column chromatography, in 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, 1H, J = 3.0 Hz), 8.13 (dd, 1H, J =

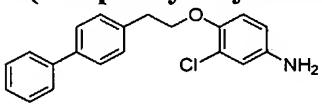
2.8 and 9.2 Hz), 7.57-7.60 (m, 4H), 7.40-7.46 (m, 4H), 7.35 (m, 1H), 6.95 (d, 2H, J = 9.2 Hz), 4.35 (t, 2H, J = 6.4 Hz), 3.25 (t, 2H, J = 6.8 Hz).

4-[2-(2-Methyl-4-nitro-phenoxy)-ethyl]biphenyl:



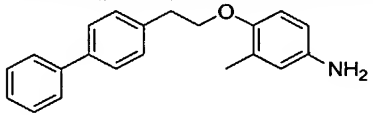
The final product was obtained as a yellow solid after column chromatography, in 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-8.09 (m, 2H), 7.55-7.59 (m, 4H), 7.44 (t, 2H, J = 8.0), 7.37 (d, 2H, J = 8.4 Hz), 6.84 (d, 2H, J = 9.2 Hz), 4.30 (t, 2H, J = 6.4 Hz), 3.20 (t, 2H, J = 6.8 Hz), 2.27 (s, 3H).

4-(2-Biphenyl-4-ylethoxy)-3-chloro-phenylamine:



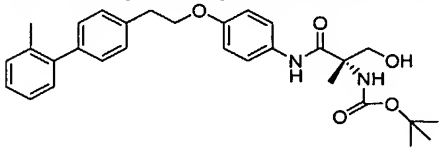
The final product was obtained as a brown oil after column chromatography, in 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.60 (m, 5H), 7.46-7.38 (m, 4H), 6.75 (m, 2H), 6.52 (dd, 1H, J = 2.8 and 8.8), 4.17 (t, 2H, J = 7.6 Hz), 3.15 (t, 2H, J = 7.2 Hz).

4-(2-Biphenyl-4-ylethoxy)-3-methyl-phenylamine:



The final product was obtained as an off white solid after column chromatography, in 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.58 (m, 4H), 7.39-7.43 (m, 2H), 7.34 (d, 3H, J = 8.4 Hz), 6.64 (d, 1H, J = 8.8 Hz), 6.50 (d, 1H, J = 3.2 Hz), 6.50 (dd, 1H, J = 2.8 and 8.4), 4.10 (t, 2H, J = 7.2 Hz), 3.09 (t, 2H, J = 7.2 Hz), 2.13 (s, 3H).

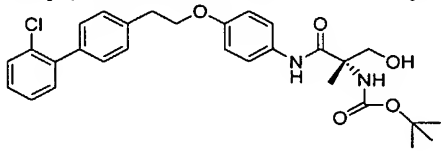
(2-Hydroxy-1-methyl-1-{4-[2-(2'-methyl-biphenyl-4-yl)-ethoxy]-phenyl carbamoyl}-ethyl)-carbamic acid tert-butyl ester:



The final product was obtained as an off white solid after column chromatography, in 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, 2H, J = 6.4 and 9.4 Hz), 7.31-7.33 (m, 2H), 7.28 (s, 2H), 7.22–7.26 (m, 4H), 6.88 (d, 1H, J = 8.8 Hz),

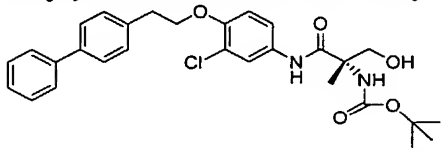
4.2 (t, 2H, J = 7.2 Hz), 3.78 (d, 1H, J = 12.0 Hz), 3.56 (d, 1H, J = 10.8 Hz), 3.13 (t, 2H, J = 7.2 Hz), 2.28 (s, 3H), 1.58 (s, 3H), 1.46 (s, 9H).

(1-{4-[2-(2'-Chloro-biphenyl-4-yl)-ethoxy]-phenyl carbamoyl}-2-hydroxy-1-methyl-ethyl)-carbamic acid tert-butyl ester:



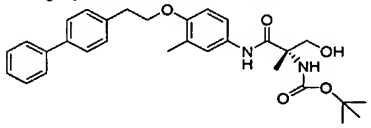
The final product was obtained as an off white oil after column chromatography, in 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 1H), 7.46 (dd, 1H, J = 7.2 and 8.8 Hz), 7.37-7.43 (m, 3H), 7.27-7.35 (m, 4H), 7.26 (s, 1H), 6.88 (d, 2H, J = 9.2 Hz), 4.21 (t, 2H, J = 7.2 Hz), 4.08 (br.s, 1H), 3.557 (d, 1H, J = 10.8 Hz), 3.14 (t, 2H, J = 7.2 Hz), 1.58 (s, 3H), 1.46 (s, 9H).

{1-[4-(2-Biphenyl-4-yl-ethoxy)-3-chloro-phenylcarbamoyl]-2-hydroxy-1-methyl-ethyl}-carbamic acid tert-butyl ester:



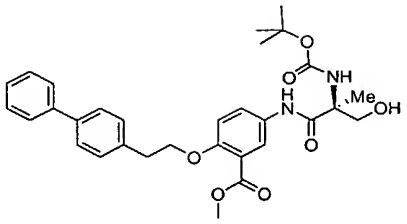
The final product was obtained as an off white solid after column chromatography, in 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.53-7.59 (m, 4H), 7.38-7.44 (m, 4H), 7.30–7.35 (m, 2H), 6.84 (d, 1H, J = 8.8 Hz), 4.21 (t, 2H, J = 7.2 Hz), 4.06 (br.s, 1H), 3.6 (s, 1H), 3.17 (t, 2H, J = 7.2 Hz), 1.56 (s, 3H), 1.44 (s, 9H).

{1-[4-(2-Biphenyl-4-yl-ethoxy)-3-methyl-phenylcarbamoyl]-2-hydroxy-1-methyl-ethyl}-carbamic acid tert-butyl ester:



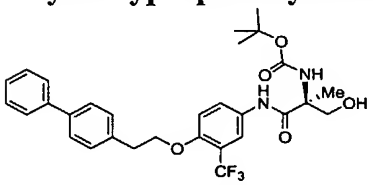
The final product was obtained as an off white solid after column chromatography, in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.59 (m, 4H), 7.43 (t, 2H, J = 7.6 Hz), 7.36 (d, 3H, J = 8.4 Hz), 7.26 (br. s, 2H), 6.76 (d, 1H, J = 8.4 Hz), 4.18 (t, 2H, J = 6.4 Hz), 3.56 (br.s, 1H), 3.31 (s, 1H), 3.14 (t, 2H, J = 6.8 Hz), 2.19 (s, 3H), 1.57 (s, 3H), 1.46 (s, 9H).

***tert*-Butyl (*S*)-2-(4-(4-phenylphenethyloxy)-3-(methylformyl)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate:**



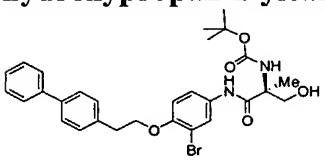
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, 1H, J = 2.7 Hz), 7.65 (dd, 1H, J = 8.8 Hz, J = 2.7 Hz), 7.50-7.60 (m, 4H), 7.28-7.46 (m, 5H), 6.83 (d, 1H, J = 8.8 Hz), 5.59 (br s, 1H), 4.53 (br t, 1H), 4.25 (t, 2H, J = 6.8 Hz), 3.87 (s, 3H), 3.53-3.62 (m, 1H), 3.18 (t, 2H, J = 6.8 Hz), 3.16-3.18 (m, 1H), 1.57 (s, 3H), 1.47 (s, 9H).

tert-Butyl (_S_)-2-(4-(4-phenyl)phenethyloxy)-3-(trifluoromethyl) phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate:



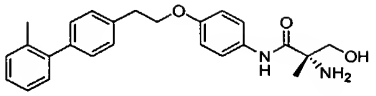
The product was obtained as a thick colorless oil in 45% (300 mg) yield over two steps from 2-biphenylethanol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (br s, 1H), 7.70 (d, 1H, J = 2.7 Hz), 7.64 (dd, 1H, J = 8.8 Hz, J = 2.7 Hz), 7.52-7.60 (m, 4H), 7.30-7.46 (m, 5H), 6.94 (d, 1H, J = 8.8 Hz), 5.60 (br s, 1H), 4.25 (t, 2H, J = 6.8 Hz), 4.04-4.14 (m, 1H), 3.50-3.60 (m, 1H), 3.17 (t, 2H, J = 6.8 Hz), 1.57 (s, 3H), 1.47 (s, 9H).

tert-Butyl (_S_)-2-(4-(4-phenylphenethyloxy)-3-bromophenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate:



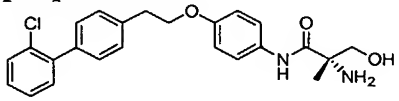
The product was obtained as a thick colorless oil in 40% (385 mg) yield over two steps from 2-biphenylethanol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (br s, 1H), 7.7 8 (d, 1H, J = 2.3 Hz), 7.53-7.62 (m, 5H), 7.30-7.46 (m, 5H), 6.83 (d, 1H, J = 8.8 Hz), 5.60 (br s, 1H), 4.22 (t, 2H, J = 6.8 Hz), 4.06-4.12 (m, 1H), 3.58 (br d, 1H), 3.20 (t, 2H, J = 6.8 Hz), 1.58 (s, 3H), 1.46 (s, 9H).

2-Amino-3-hydroxy-2-methyl-_N_-{4-[2-(2'-methyl-biphenyl-4-yl)-ethoxy]-phenyl}-propionamide:



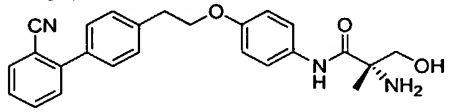
The compound was obtained as a white solid after HPLC purification. Yield: 93 %, (92mg). MS (ESI, $M+H^+$) = 404.4

2-Amino-*N*-{4-[2-(2'-Chloro-biphenyl-4-yl)-ethoxy]-phenyl}-3-hydroxy-2-methyl-propionamide:



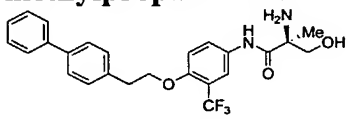
The compound was obtained as a white solid after HPLC purification. Yield: 84 %, (68mg). MS (ESI, $M+H^+$) = 425.7

(1-{4-[2-(2'-Cyano-biphenyl-4-yl)-ethoxy]-phenylcarbamoyl}-2-hydroxy-1-methyl-ethyl)-carbamic acid tert-butyl ester:



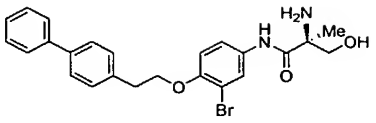
The final product was obtained as an off white oil after column chromatography, in 80% yield. MS (ESI, $M+H^+$) = 416.6, ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.63 (m, 3H), 7.53 (br. s, 2H), 7.48-7.51 (m, 4H), 6.97 (d, 2H, J = 9.2 Hz), 5.77 (t, 1H, J = 5.2 Hz), 4.24 (t, 2H, J = 6.8 Hz), 3.96 (dd, 1H, J = 12.0 and 5.2 Hz), 3.628 (dd, 1H, J = 11.6 and 4.8 Hz), 3.12 (t, 2H, J = 6.8 Hz), 1.47 (s, 3H).

(*S*)-*N*-(4-(4-Phenylphenethyloxy)-3-(trifluoromethyl)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



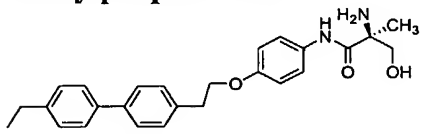
The product was obtained as a white solid in 70% (66 mg) yield. MS (ESI, $M+H^+$) = 459.7; ^1H NMR (400 MHz, DMSO-d_6) δ 10.01 (br s, 1H), 8.180 (br s, 2H), 7.89 (d, 1H, J = 2.4 Hz), 7.82 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 7.58-7.67 (m, 4H), 7.30-7.49 (m, 6H), 5.80 (br s, 1H), 4.32 (t, 2H, J = 6.7 Hz), 3.95 (br d, 1H), 3.62 (br d, 1H), 3.09 (t, 2H, J = 6.7 Hz), 1.48 (s, 3H).

(*S*)-*N*-(4-(4-phenylphenethyloxy)-3-bromophenyl)-2-amino-3-hydroxy-2-methylpropanamide:



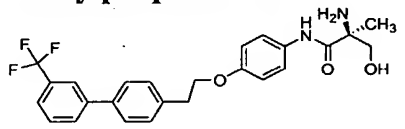
The product was obtained as a white solid in 60% (50 mg) yield. MS (ESI, $M+H^+$) = 469.4 and 471.4.

(*S*)-*N*-(4-(4-(4-Ethylphenyl)phenethyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



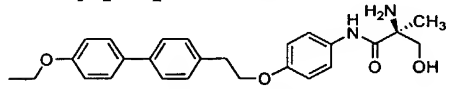
MS (ESI, $M+H^+$) = 419; ^1H NMR (400 MHz, DMSO-d_6) δ 9.74 (bs, 1H), 8.1 (bs, 1H), 7.55 (m, 4H), 7.47 (d, 2H), 7.37 (d, 2H), 7.26 (d, 2H), 6.93 (d, 2H), 5.74 (bs, 1H), 4.16 (t, 2H), 3.95 (bd, 1H), 3.6 (bd, 1H), 3.04 (t, 2H), 2.6 (q, 2H), 1.73 (m, 4H), 1.45 (s, 3H), 1.19 (t, 3H).

(*S*)-*N*-(4-(4-(4-Trifluoromethylphenyl)phenethyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



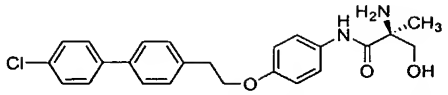
MS (ESI, $M+H^+$) = 459; ^1H NMR (400 MHz, DMSO-d_6) δ 9.74 (br s, 1H), 8.1 (br s, 2H), 7.95 (m, 2H), 7.68 (m, 3H), 7.47 (m, 3H), 6.93 (m, 2H), 5.74 (br s, 1H), 4.19 (t, 2H), 3.95 (m, 1H), 3.6 (m, 1H), 3.04 (t, 2H), 2.6 (q, 2H), 1.45 (s, 3H).

(*S*)-*N*-(4-(4-(4-ethoxyphenyl)phenethyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



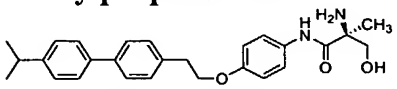
MS (ESI, $M+H^+$) = 435; ^1H NMR (400 MHz, DMSO-d_6) δ 9.73 (bs, 1H), 8.10 (bs, 2H), 7.57 (m, 2H), 7.46 (m, 2H), 7.32 (t, 1H), 7.22 (m, 1H), 6.94 (m, 2H), 5.75 (t, 1H), 4.19 (t, 2H), 4.04 (q, 2H), 3.93 (m, 1H), 3.61 (m, 1H), 3.07 (t, 2H), 1.45 (s, 3H), 1.32 (t, 3H).

(*S*)-*N*-(4-(4-(4-Chlorophenyl)phenethyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide trifluoroacetic acid salt



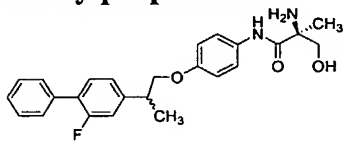
MS (ESI, M+H$^+$) = 424; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.73 (s, 1H), 8.10 (bs, 2H), 7.69 (m, 2H), 7.61 (s, 1H), 7.49 (m, 3H), 7.37 (t, 1H), 7.33 (m, 1H), 6.94 (d, 2H), 5.75 (t, 1H), 4.20 (t, 2H), 4.04 (q, 2H), 3.93 (m, 1H), 3.61 (m, 1H), 3.08 (t, 2H), 1.45 (s, 3H).

(*S*)-*N*-(4-(4-(4-Isopropylphenyl)phenethyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



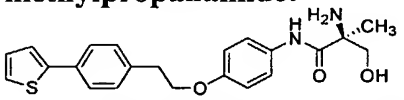
MS (ESI, M+H$^+$) = 433; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.73 (s, 1H), 8.11 (br s, 2H), 7.59 (d, 1H), 7.41-7.34 (m, 3H), 7.2 (d, 1H), 6.9 (d, 2H), 5.65 (br s, 1H), 4.18 (t, 2H), 3.93 (d, 1H), 3.61 (d, 1H), 3.04 (t, 2H), 2.95 (q, 1H), 1.45 (s, 3H), 1.24 (d, 6H).

(*S*)-*N*-(4-(2-(4-Phenyl-3-fluorophenyl)propoxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



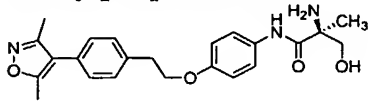
MS (ESI, M+H$^+$) = 423; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.74 (br s, 1H), 8.1 (br s, 1H), 7.5 (m, 6H), 7.40 (m, 2H), 7.28 (m, 2H), 6.93 (d, 2H), 5.74 (br s, 1H), 4.1-4.0 (m, 2H), 3.9 (m, 1H), 3.65 (m, 1H), 3.28 (m, 2H), 1.47 (s, 3H), 1.33 (d, 3H).

(*S*)-*N*-(4-(4-(Thiophen-2-yl)phenethyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



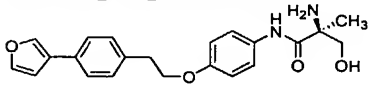
MS (ESI, M+H$^+$) = 397; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.74 (br s, 1H), 8.1 (br s, 2H), 7.60 (d, 2H), 7.50 (m, 4H), 7.36 (d, 2H), 7.12 (m, 1H), 6.95 (d, 2H), 5.74 (br s, 1H), 4.18 (t, 2H), 3.95 (br d, 1H), 3.6 (br d, 1H), 3.04 (t, 2H), 1.45 (s, 3H).

(*S*)-*N*-(4-(4-(3,5-Dimethylisoxazol-4-yl)phenethyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



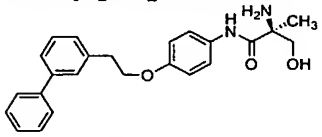
MS (ESI, M+H$^+$) = 410; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (br s, 1H), 8.13 (br s, 2H), 7.50 (d, 2H), 7.41 (d, 2H), 7.3 (d, 2H), 6.9 (d, 2H), 4.22 (t, 2H), 3.94 (d, 1H), 3.6 (d, 1H), 3.07 (t, 2H), 2.4 (s, 3H), 2.2 (s, 2H), 1.48 (s, 3H).

(*S*)-*N*-(4-(4-(Furan-3-yl)phenethyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



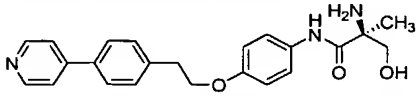
MS (ESI, M+H$^+$) = 424; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 1H), 8.10 (br s, 2H), 7.69 (m, 2H), 7.61 (s, 1H), 7.49 (m, 3H), 7.37 (t, 1H), 7.33 (m, 1H), 6.94 (d, 2H), 5.75 (t, 1H), 4.20 (t, 2H), 4.04 (q, 2H), 3.93 (m, 1H), 3.61 (m, 1H), 3.08 (t, 2H), 1.45 (s, 3H).

(*S*)-*N*-(4-(4-(3-Phenyl)phenethyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



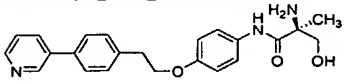
MS (ESI, M+H$^+$) = 391; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (s, 1H), 8.10 (br s, 2H), 7.66 (d, 2H), 7.61 (s, 1H), 7.55-7.30 (m, 4H), 6.94 (d, 2H), 5.75 (bs, 1H), 4.25 (t, 2H), 3.93 (d, 1H), 3.65 (d, 1H), 3.08 (t, 2H), 1.45 (s, 3H).

(*S*)-*N*-(4-(4-(Pyridin-4-yl)phenethyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



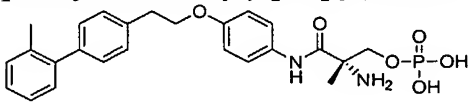
MS (ESI, M+H$^+$) = 392; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.74 (br s, 1H), 8.67 (br s), 8.19 (br s, 2H), 8.12 (br s, 2H), 7.8 (m, 2H), 7.5 (m, 4H), 6.9 (m, 2H), 6.95 (d, 2H), 5.74 (br s, 1H), 4.2 (t, 2H), 3.95 (br d, 1H), 3.04 (t, 2H), 1.45 (s, 3H).

(*S*)-*N*-(4-(4-(Pyridin-3-yl)phenethyloxy)phenyl)-2-amino-3-hydroxy-2-methylpropanamide:



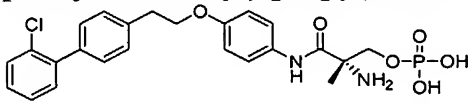
MS (ESI, M+H$^+$) = 392; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (s, 1H), 9.0 (s, 1H), 8.65 (m, 1H), 8.3 (d, 2H), 8.07 (br s, 2H), 7.75 (m, 2H), 7.50 (m, 4H), 6.95 (d, 2H), 4.2 (t, 2H), 3.95 (d, 1H), 3.6 (d, 2H), 3.1 (t, 2H), 1.45 (s, 3H).

(*S*)-Phosphoric acid mono-(2-amino-2-{4-[2-(2'-methyl-biphenyl-4-yl)-ethoxy]-phenylcarbamoyl}-propyl) ester:



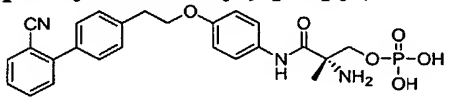
The compound was obtained as a white solid after HPLC purification. Yield: 65%, (41mg). MS (ESI, $M+H^+$) = 485.5

(*S*)-Phosphoric acid mono-(2-amino-2-{4-[2-(2'-chloro-biphenyl-4-yl)-ethoxy]-phenylcarbamoyl}-propyl) ester:



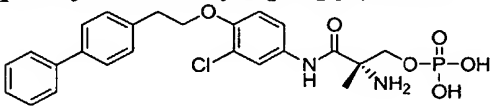
The compound was obtained as a white solid after HPLC purification. Yield: 79 %, (25mg). MS (ESI, $M+H^+$) = 505.2

(*S*)-Phosphoric acid mono-(2-amino-2-{4-[2-(2'-cyano-biphenyl-4-yl)-ethoxy]-phenylcarbamoyl}-propyl) ester:



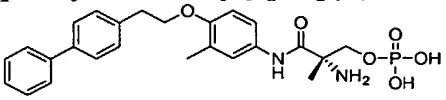
The compound was obtained as a white solid after HPLC purification. Yield: 22 %, (4mg). MS (ESI, $M+H^+$) = 496.6

(*S*)-Phosphoric acid mono-(2-amino-2-[4-(2-biphenyl-4-yl-ethoxy)-3-chloro-phenylcarbamoyl]-propyl} ester:



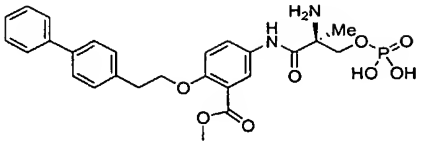
The compound was obtained as a white solid after HPLC purification. Yield: 30%, (70mg). MS (ESI, $M+H^+$) = 504.9

(*S*)-Phosphoric acid mono-(2-amino-2-[4-(2-biphenyl-4-yl-ethoxy)-3-methyl-phenylcarbamoyl]-propyl} ester:



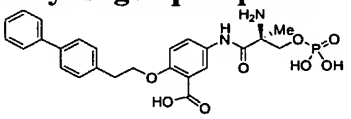
The compound was obtained as a white solid after HPLC purification. Yield: 10%, (28mg). MS (ESI, $M+H^+$) = 484.2

(*S*)-2-(4-(4-Phenylphenethyloxy)-3-(methylformyl)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



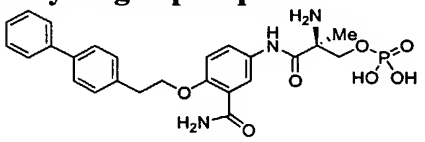
The product was obtained as a white solid in 72% (10.0 mg) yield over two steps. MS (ESI, $M+H^+$) = 529.1.

(*S*)-2-(4-(4-Phenylphenethyloxy)-3-(formyl)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



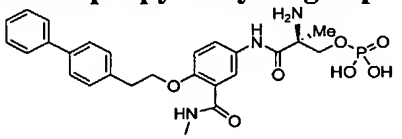
The product was obtained as a white solid in 90% (6.0 mg) yield over two steps. MS (ESI, $M+H^+$) = 515.0

(*S*)-2-(4-(4-Phenylphenethyloxy)-3-(carbamoyl)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



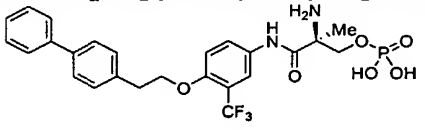
The product was obtained as a white solid in 20% (1.0 mg) yield over four steps. MS (ESI, $M+H^+$) = 514.6

(*S*)-2-(4-(4-Phenylphenethyloxy)-3-(methylcarbamoyl)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



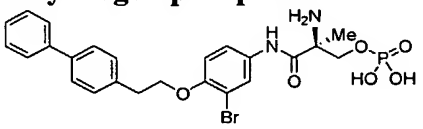
The product was obtained as a white solid in 25% (1.0 mg) yield over four steps. MS (ESI, $M+H^+$) = 528.6

(*S*)-2-(4-(4-Phenylphenethyloxy)-3-(trifluoromethyl)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



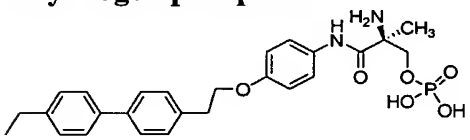
The product was obtained as a white solid in 70% (65.0 mg) yield over four steps. MS (ESI, $M+H^+$) = 539.7

(*S*)-2-(4-(4-Phenylphenethyloxy)-3-bromophenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



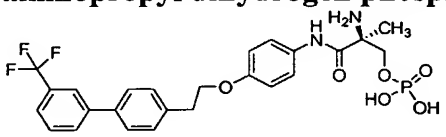
The product was obtained as a white solid in 69% (65.0 mg) yield over four steps. MS (ESI, $M+H^+$) = 548.9 and 550.9

(*S*)-2-(4-(4-(4-Ethylphenyl)phenethyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



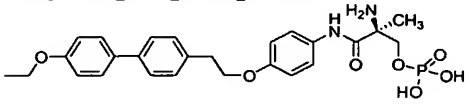
This compound was synthesized from *tert*-butyl (S)-2-(4-(4-(4-ethylphenyl)phenethyloxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate (65 mg) to yield 21 mg solid product over two steps. MS (ESI, $M+H^+$) = 499; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (br s, 1H), 7.54 (m, 6H), 7.37 (d, 2H), 7.26 (d, 2H), 6.92 (d, 2H), 4.21 (m, 1H), 4.17 (t, 2H), 4.1 (m, 1H), 3.75 (s, 3H), 3.04 (t, 2H), 2.58 (q, 2H), 1.45 (s, 3H), 1.17 (t, 3H).

(*S*)-2-(4-(4-(4-Trifluoromethylphenyl)phenethyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



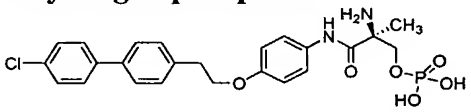
This compound was synthesized from tert-butyl (S)-2-(4-(4-(4-trifluoromethylphenyl)phenethyloxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate (70 mg) to yield 27 mg solid product over two steps. MS (ESI, $M+H^+$) = 539; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (br s, 1H), 7.95 (m, 2H), 7.69 (d, 4H), 7.5 (d, 2H), 7.4 (d, 2H), 6.9 (d, 2H), 4.21 + 4.19 (overlapping signals, 3H), 4.05 (m, 1H), 3.06 (t, 2H), 1.45 (s, 3H).

(*S*)-2-(4-(4-(4-Ethoxyphenyl)phenethyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



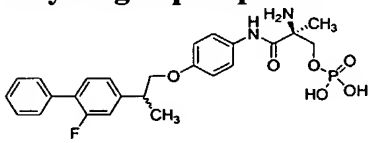
MS (ESI, M+H$^+$) = 515; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (br s, 1H), 7.57 (m, 2H), 7.50 (m, 2H), 7.30 (m, 2H), 6.97 (d, 1H), 6.91 (t, 2H), 4.2-4.0 (m, 2H), 4.10 (t, 2H), 3.1 (m, 2H), 3.0 (m, 2H), 1.45 (s, 3H), 1.32 (t, 3H).

(*S*)-2-(4-(4-(4-Chlorophenyl)phenethyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



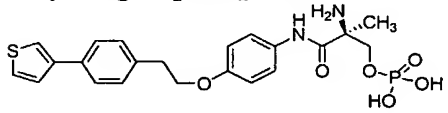
MS (ESI, M+H$^+$) = 505.7; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 7.69 (m, 2H), 7.61 (s, 1H), 7.49 (m, 3H), 7.37 (t, 1H), 7.33 (m, 1H), 6.94 (d, 2H), 4.3-4.0 (m overlapping signals, 4H), 3.08 (t, 2H), 3.00 (m, 2H), 1.45 (s, 3H).

(*S*)-2-(4-(2-(4-Phenyl-3-fluorophenyl)propoxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



This compound was synthesized from *tert*-butyl (S)-2-(4-(2-(4-phenyl-3-fluorophenyl)propoxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate (135 mg) to yield 72 mg solid product over two steps. MS (ESI, M+H$^+$) = 503; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (br s, 1H), 8.6 (br s, 2H), 7.54-7.26 (m, 10H), 6.92 (d, 2H), 4.28 (t, 1H), 4.1-3.9 (m, 3H), 4.1 (m, 1H), 3.28 (m, 2H), 1.49 (s, 3H), 1.35 (d, 3H).

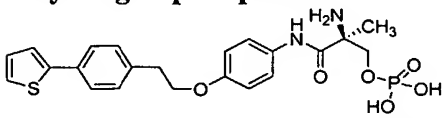
(*S*)-2-(4-(4-(Thiophen-3-yl)phenethyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



The starting material, 2-(4-(thiophen-3-yl)phenyl)ethanol, was synthesized as follows: In a sealed vessel was combined 2-(4-bromophenyl)ethanol (70 μL), 4,4,5,5-tetramethyl-2-(thiophen-3-yl)-1,3,2-dioxaborolane (126 mg), K_2CO_3 (207 mg), catalytic $Pd(PPh_3)_4$, 4.5 mL THF, and 0.5 mL H_2O. The vessel was heated in an oil bath at 60 °C overnight. The reaction mixture was diluted with water and DCM. The organic layer was concentrated to yield 2-(4-(thiophen-3-yl)phenyl)ethanol (80 mg) as a solid white product. 80 mg tert-butyl (S)-2-(4-(4-(thiophen-3-yl)phenethyloxy)phenylcarbamoyl)-1-hydroxypropan-2-ylcarbamate was synthesized following the general procedure employing 2-(4-(thiophen-3-yl)phenyl)ethanol (200 mg), *N*-(Boc)-α-methylserine (175 mg), HATU (375 mg), and DIPEA (430 uL). MS (ESI, M+Na$^+$) = 519. 2.6 mg of the

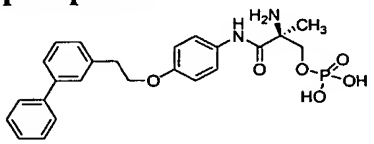
phosphate was then synthesized from the carbamate (40 mg) as a solid white solid. MS (ESI, $M+H^+$) = 477; ^1H NMR (400 MHz, DMSO-d_6) δ 9.96 (br s, 1H), 7.81 (m, 1H), 7.65 (m, 3H), 7.5 (m, 3H), 7.3 (m, 2H), 6.9 (m, 2H), 4.28 (m, 1H), 4.17 (m, 2H), 4.06 (m, 1H), 3.04 (t, 2H), 1.48 (s, 3H).

(*S*)-2-(4-(4-(Thiophen-2-yl)phenethyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



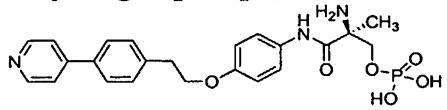
^1H NMR (400 MHz, DMSO-d_6) δ 9.98 (br s, 1H), 8.64 (br s, 3H), 7.84 (s, 1H), 7.65 (m, 3H), 7.52 (m, 3H), 7.36 (d, 2H), 6.9 (d, 2H), 4.21 (overlapping signals, 3H), 4.17 (m, 1H), 3.04 (t, 2H), 2.58 (q, 2H), 1.45 (s, 3H).

(S)-2-(4-(3-Phenylphenethyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



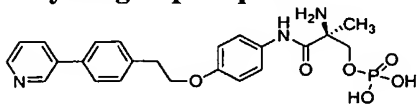
^1H NMR (400 MHz, DMSO-d_6) δ 9.9 (s, 1H), 7.66 (d, 2H), 7.61 (s, 1H), 7.55-7.30 (m, 4H), 6.94 (d, 2H), 4.25 (t, 2H), 4.2 (m, 1H), 4.05 (m, 1H), 3.08 (t, 2H), 1.45 (s, 3H).

(*S*)-2-(4-(4-(Pyridin-4-yl)phenethyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



^1H NMR (400 MHz, D_2O + CD_3OD) δ 8.7 (m), 8.2 (m), 7.84 (d, 2H), 7.55 (d, 2H), 7.4 (d, 2H), 6.9 (d, 2H), 4.30 (t, 2H), 4.05 (m, 1H), 3.92 (m, 1H), 3.15 (t, 2H), 1.42 (s, 3H).

(*S*)-2-(4-(4-(Pyridin-3-yl)phenethyloxy)phenylcarbamoyl)-2-aminopropyl dihydrogen phosphate:



^1H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.95 (s, 1H), 8.65 (br s, 1H), 8.28 (d, 2H), 7.75 (m, 2H), 7.60 (m, 1H), 7.5 (t, 3H), 6.95 (d, 2H), 4.2 (m, 3H), 3.95 (m, 1H), 3.10 (m, 2H), 1.45 (s, 3H).

Example 10: Lymphopenia Assay

Several of the compounds described herein were evaluated for the ability to induce lymphopenia in mice. Male C57Bl/6 mice were divided into groups of three. A control group received the 3% BSA vehicle only. The other groups received a single dose of either a specified dose of test compound in vehicle administered orally (PO). After 6 hours, the mice were anesthesized with isoflurane and approximately 250 μL of blood was removed from the retroorbital sinus and collected in an EDTA microtainer, mixed with an anticoagulant and placed on a tilt table until complete blood count (CBC) analysis. Figure 1 shows the results of the analysis for total lymphocyte count for different doses of compounds 10, 13 and 14. The results show that all three compounds, when dosed orally, are able to induce lymphopenia in mice relative to control.

Example 11: Binding to S1P1 or S1P3 Receptors

The ability of several of the compounds described herein to bind to the S1P1 or S1P3 receptor was also tested as follows.

For the membrane preparation, plasmid DNA was transfected into HEK 293 T cells using the FuGENE 6 transfection protocol (publicly available by Roche). Briefly, subconfluent monolayers of HEK 293 T cells were transfected with the DNA mixture containing FuGENE 6 (using a 1:3 ratio). The dishes containing the cells were then placed in a tissue culture incubator (5% CO_2, 37°C). The cells were harvested 48 hours after addition of the DNA by scraping in HME buffer (in mM: 20 HEPES, 5 $MgCl_2$, 1 EDTA, pH 7.4, 1 mM PMSF) containing 10% sucrose on ice, and disrupted using a Dounce homogenizer. After centrifugation at 800 × *g*, the supernatant was diluted with HME without sucrose and centrifuged at 17,000 × *g* for 1 hour. This crude membrane pellet was resuspended in HME with sucrose, aliquoted, and snap-frozen by immersion in liquid nitrogen. The membranes were stored at -70 C. Protein concentration was determined spectroscopically by Bradford protein assay.

For the binding assay, [^{33}P]sphingosine 1-phosphate (obtained from American Radiolabeled Chemicals, Inc) was added to membranes in 200 μl in 96-well plates with assay concentrations of 2.5 pM [^{33}P]sphingosine 1-phosphate, 4 mg/ml BSA, 50 mM HEPES, pH 7.5, 100 mM NaCl, 5 mM MgCl2, and 5 μg of protein. Binding was performed for 60 minutes at room temperature with gentle mixing and terminated by collecting the membranes onto GF/B filter plates. After drying the filter plates for 10 minutes, 50 μl of Microscint 40 was added to each well, and filter-bound radionuclide was measured on a Packard Top Count. Nonspecific binding was defined as the amount of radioactivity remaining in the presence of excess of unlabeled S1P. The results fo the foregoing binding assays are presented in Table 1 provided below.

Table 1: IC50 Values for Binding to S1P1 or S1P3 Receptors

COMPOUND No.	S1P1 IC_{50} (nM)	S1P3 IC_{50} (nM)
301	1000	>10000
302	2.4	343
303	3.5	50
304	2000	>10000
305	250	5000
306	240	8000
307	32	1100
308	23	5000
309	8.7	511
310	23	2150
311	15	164
312	166	1100
313	2.2	135
314	56	59
315	2000	10000
316	4000	>10000
317	90	>10000
318	0.84	160
319	650	>10000
320	218	833
321	17.9	6333
322	0.65	50
323	>10000	>10000
324	114	1200
325	167	3500
326	2.5	220
327	4000	>10000
328	22.1	2500
329	8	315
330	2200	>10000
331	3800	>10000
332	3.4	2000
333	12	1040
334	>10000	>10000
335	4500	>10000
336	2000	>10000
337	166	130
338	21	>10000
339	>10000	>10000
340	0.55	5025
341	1.3	1000

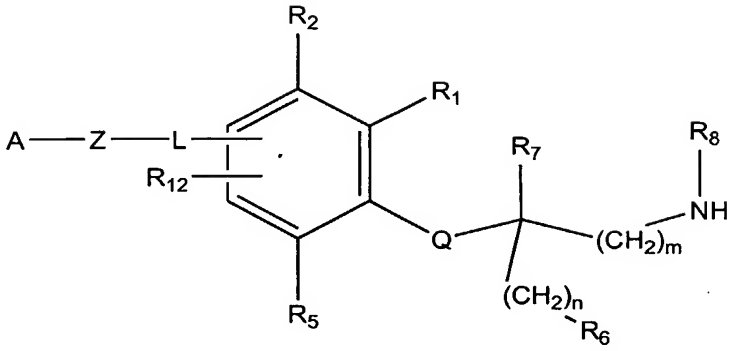
342	>10000	>10000
343	0.8	285
344	150	>1000
345	500	>1000
346	6	3250
347	1000	>10000
348	6.5	500
349	3.5	50

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

Claims

1. A compound of Formula IV:



(IV)

wherein:

L is alkoxy, a covalent bond, substituted or unsubstituted alkyl, alkylcarbonyl, thioether, alkylsulfonyl, alkylcarbonylamino, alkylaminocarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, or substituted or unsubstituted heteroaryl;

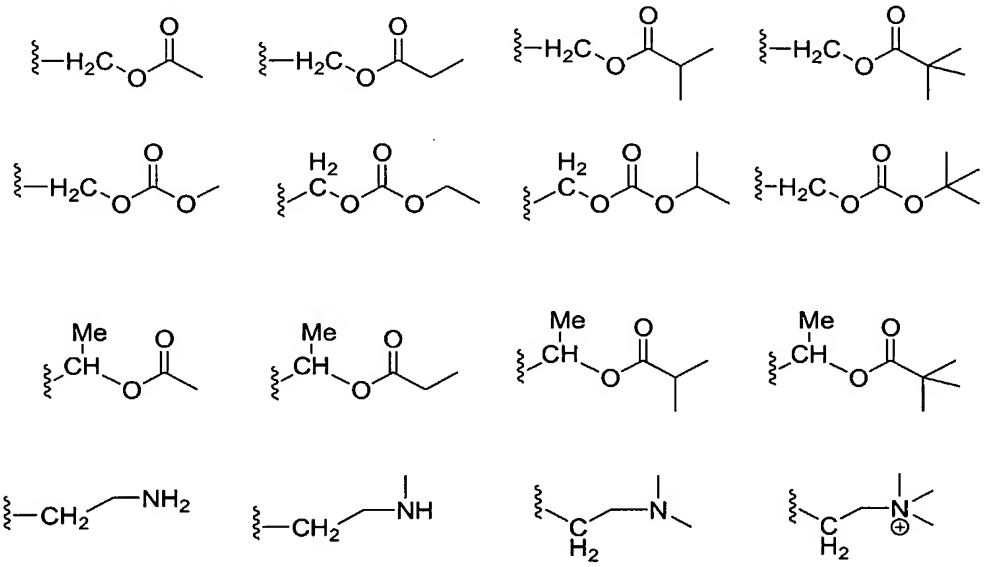
Z and A are each independently substituted or unsubstituted aryl, wherein Z and A may be linked by a covalent bond, substituted or unsubstituted alkyl, NH, alkyloxy, O, thioether, S, aminocarbonyl, carbonylamino, carbonyloxy, or oxycarbonyl;

R^1, R^2, R^5 and R^{12} are each independently selected from the group consisting of hydrogen, halogen, cyano, substituted or unsubstituted aryl, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', wherein R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2;

Q is $-CH_2NR-$, $-CH_2NR(CO)-$, $-NH(CO)-$, $-(CO)NH-$, $-(CO)-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NRSO_2-$, $-SO_2-NR-$ or heteroaryl, where R is hydrogen or straight chain or branched C_1-C_6-alkyl;

R^6 is $-OH$, $-CO_2R^9$, $-CH_2=CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-

alkyl, or a substituted or unsubstituted aryl group; R10 and R11 are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



R^7 is H, C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, aryl, or together with R8 form a C_2-C_5-alkylene or a C_2-C_5-alkenylene group;

R^8 is H or C_1-C_6-alkyl; and

m and n are each, independently, an integer from 0 to 3;

provided that when R^4 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^3 and R^5 is not hydrogen; and when R^3 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^4 and R^5 is not hydrogen; and pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein R^1 is hydrogen.

3. The compound of claim 1 or 2, wherein R^2 is hydrogen.

4. The compound of claim 1 or 2, wherein R^2 is alkyl.

5. The compound of claim 1 or 2, wherein R^2 is a halogen.

6. The compound of any one of claims 1-5, wherein R^5 is hydrogen.

7. The compound of any one of claims 1-5, wherein R^5 is a substituted or unsubstituted alkyl group or a halogen.

8. The compound of any one of claims 1-7, wherein Q is –NH-CO-.

9. The compound of any one of claims 1-7 wherein Q is –CO-NH-.

10. The compound of any one of claims 1-7 wherein Q is substituted or unsubstituted aryl group.

11. The compound of claim 1-7, wherein Q is a carbonyl group.

12. The compound of any one of claims 1-11, wherein R^6 is hydrogen, an alkoxy group, or an alkyl ether group.

13. The compound of any one of claims 1-11, wherein R^6 is a hydroxy or substituted or unsubstituted alkyl group.

14. The compound of any one of claims 1-11, wherein R^6 is a substituted or unsubstituted aryloxy group.

15. The compound of any one of claim 14, wherein substituted or unsubstituted R^6 aryloxy group is a substituted or unsubstituted phenoxy group.

16. The compound of any one of claim 15, wherein said R^6 substituted phenoxy group is substituted with one or more substituted or unsubstituted alkyl groups.

17. The compound of any one of claims 1-16, wherein R^6 is a phosphate, alkyl phosphate, cycloalkyl phosphate, phosphonate, thiophosphate, alkylthiophosphate, cycloalkylthiophosphate, or thiophosphonate.

18. The compound of any one of claims 1-11, wherein R^6 is a carboxylic acid.

19. The compound of any one of claims 1-11, wherein R^6 is a substituted or unsubstituted alkyl or aryl ester.

20. The compound of any one of claims 1-19, wherein R^7 is hydrogen, or a substituted or unsubstituted alkyl group.

21. The compound of claim 20, where said substituted R^7 alkyl group is substituted with one or more hydroxyl groups.

22. The compound of any one of claims 1-21, wherein R^8 is hydrogen.

23. The compound of any one of claims 1-21, wherein R^8 is hydroxy or substituted or unsubstituted alkyl.

24. The compound of any one of claims 1-23, wherein R^{12} is meta to Q.

25. The compound of claim 24, wherein R^{12} is cyano, hydrogen, trifluoroalkyl, or halogen.

26. The compound of any one of claims 1-23, wherein R^{12} is para to Q.

27. The compound of claim 26, wherein R^{12} is hydrogen.

28. The compound of any one of claims 1-27, wherein L is C_1-C_5 alkoxy.

29. The compound of any one of claims 1-28, wherein Z is substituted or unsubstituted phenyl.

30. The compound of any one of claims1-29, wherein A is substituted or unsubstituted phenyl.

31. The compound of any one of claims 1-29, wherein A is substituted or unsubstited heteroaryl.

32. The compound of any one of claims 31, wherein A is methylenedioxyphenyl.

33. The compound of any one of claims 1-32, wherein A is linked to Z through a single covalent bond.

34. The compound of any one of claims 1-31, wherein A is linked to Z through a covalent bond and NH to form a fused ring structure.

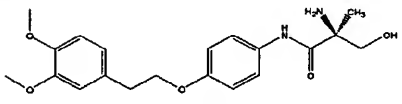
35. The compound of any one of claims 1-34, wherein said compound is an agonist of a sphingosine 1-phosphate 1 receptor.

36. The compound of claim 35, wherein said compound is a selective agonist of the sphingosine 1-phosphate 1 receptor.

37. The compound of claim 36, wherein said compound has an IC_{50} in the S1P-1 assay of about 100 nM or less.

38. The compound of claim 36, wherein said compound has an IC_{50} in the S1P-3 assay of about 100 nM or greater.

39. A compound selected from the group consisting of: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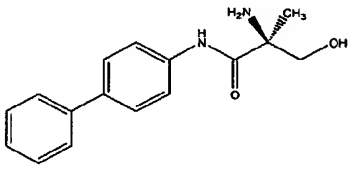
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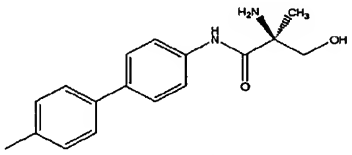
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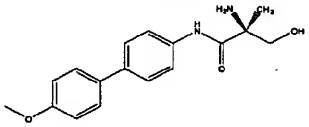
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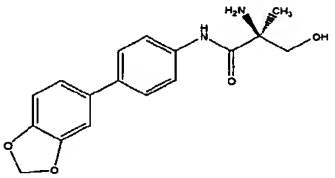
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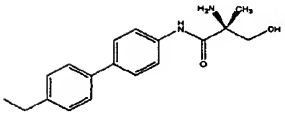
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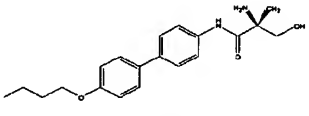
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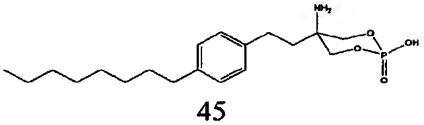
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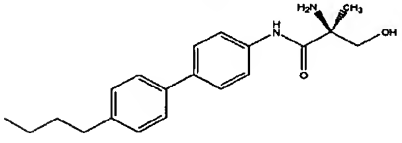
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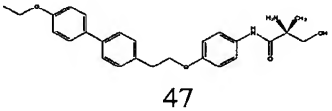
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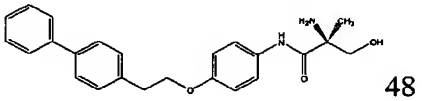
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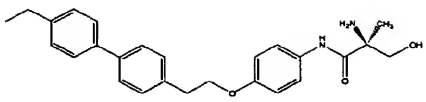
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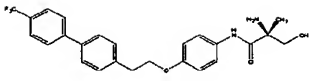
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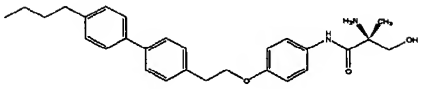
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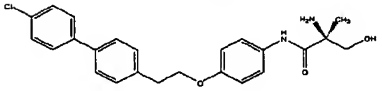
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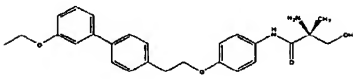
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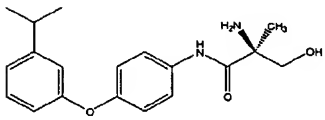
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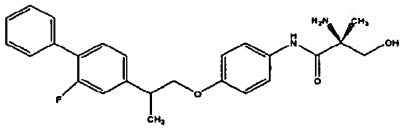
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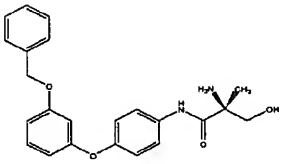
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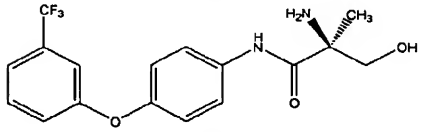
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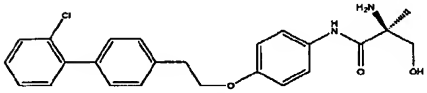
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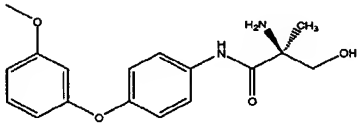
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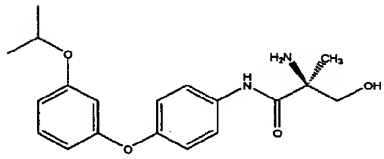
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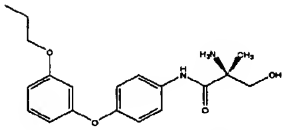
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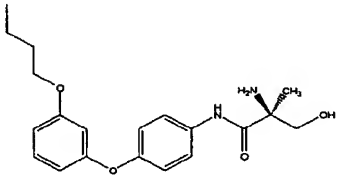
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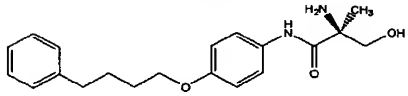
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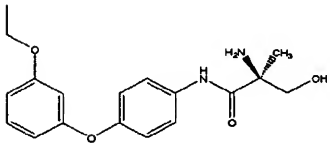
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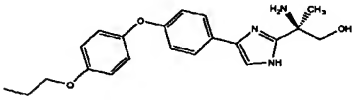
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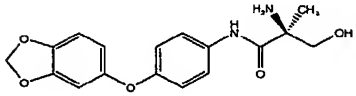
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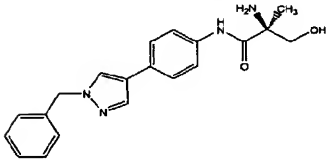
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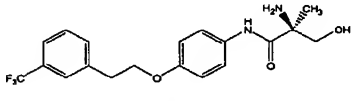
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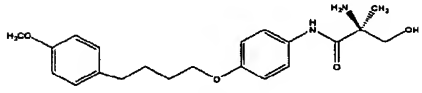
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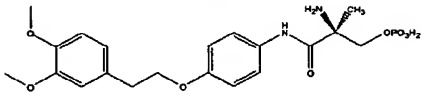
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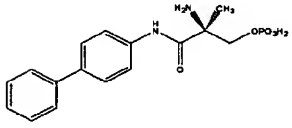
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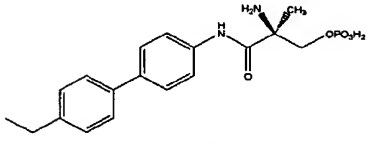
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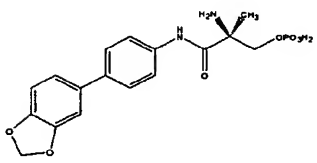

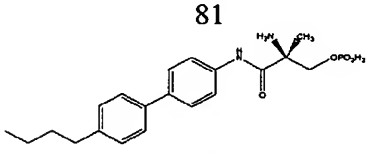
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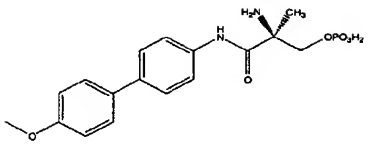
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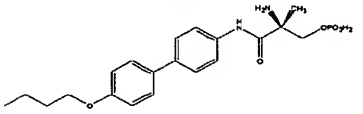
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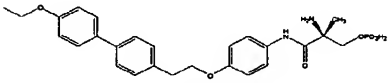
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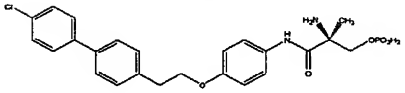
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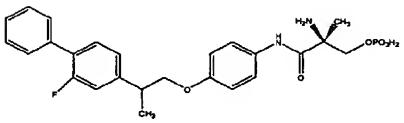
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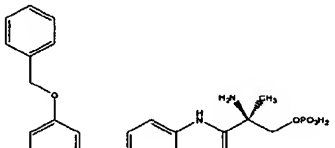
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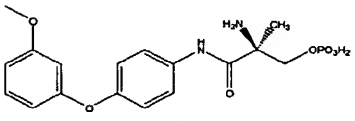
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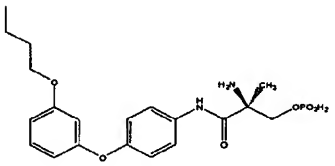
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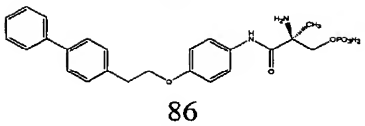
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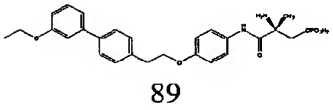
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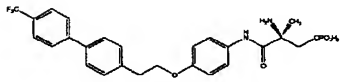
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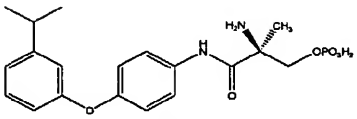
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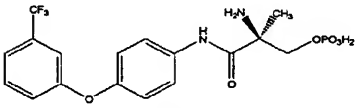
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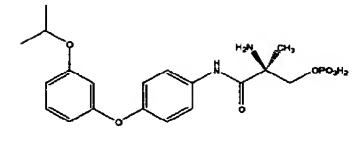
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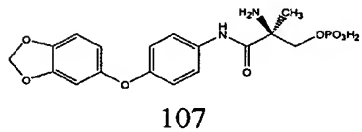
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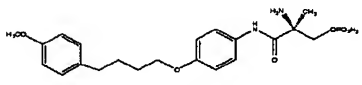
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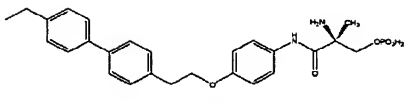
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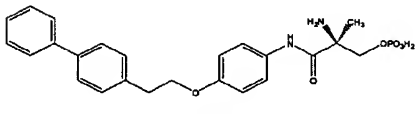
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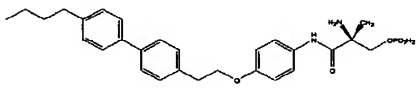
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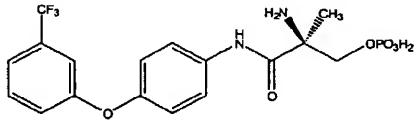
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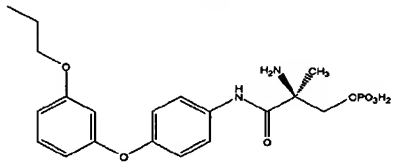
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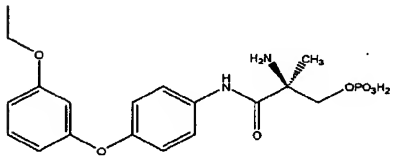
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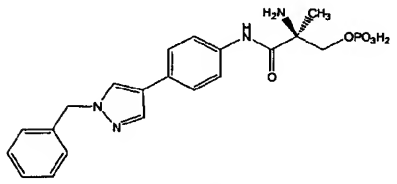
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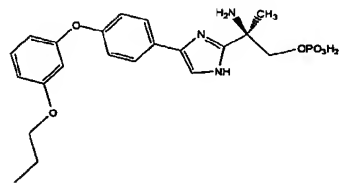
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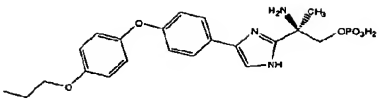

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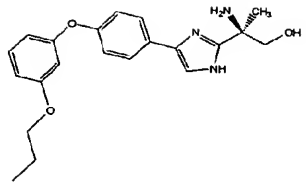

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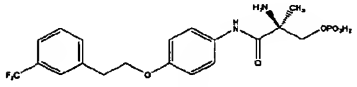

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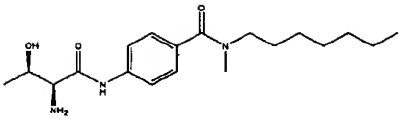

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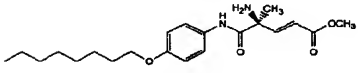

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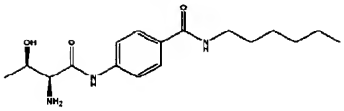

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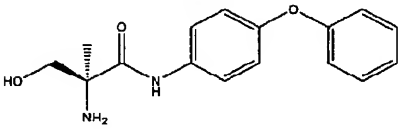

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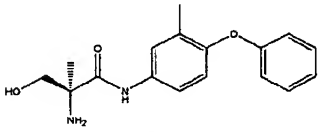

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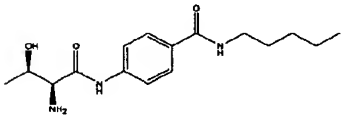

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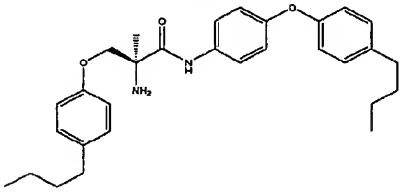

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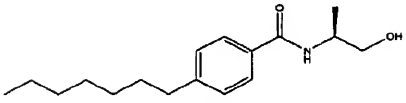

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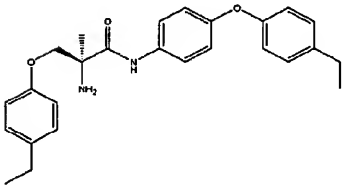

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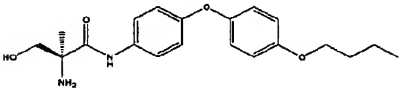

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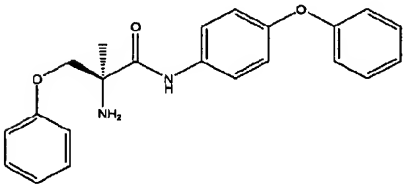

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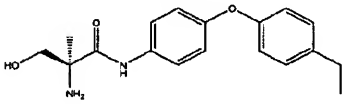

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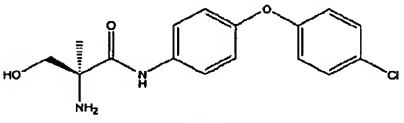

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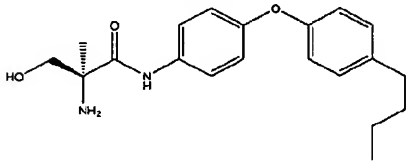

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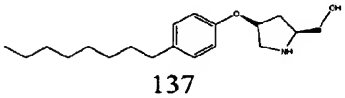

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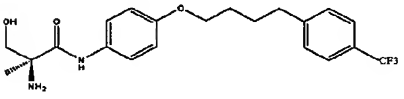

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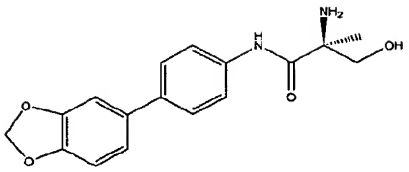

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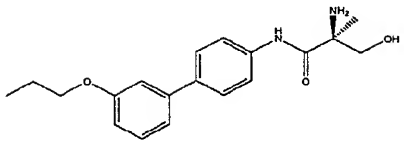

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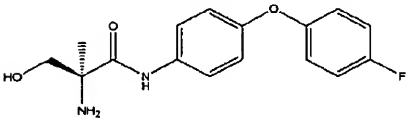

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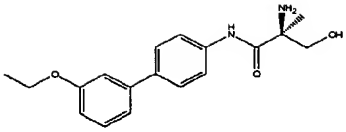

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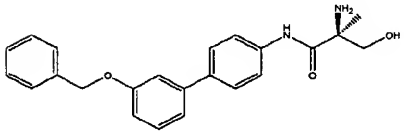

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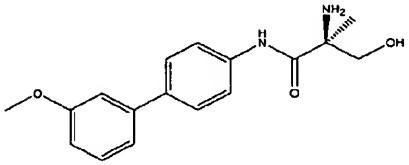

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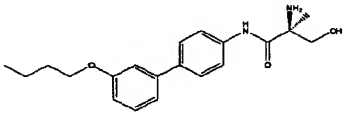

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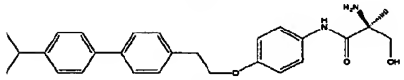

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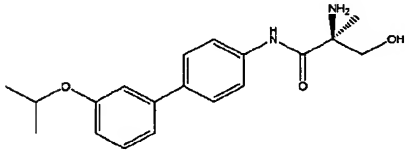

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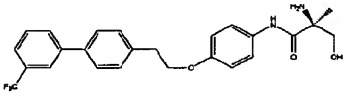

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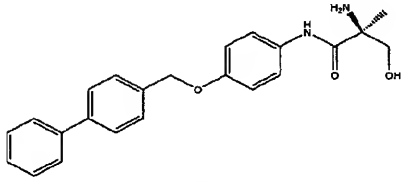

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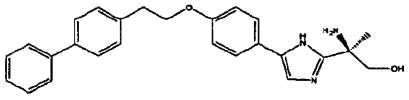

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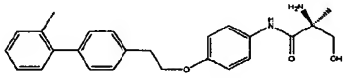

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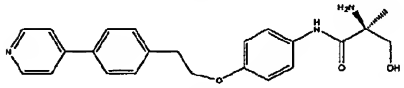

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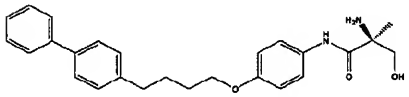

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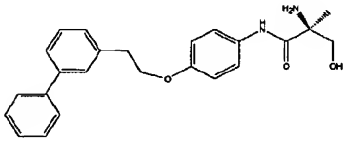

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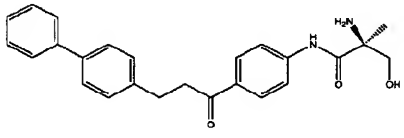

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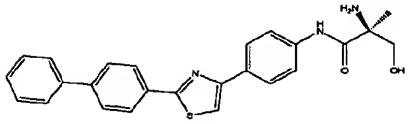

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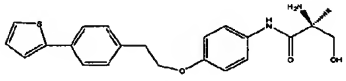

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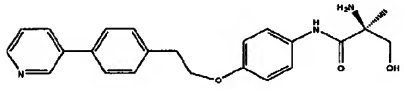

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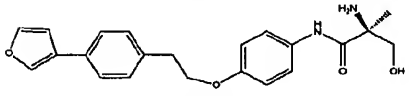

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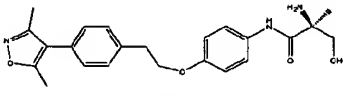

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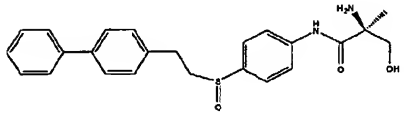

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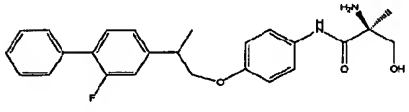

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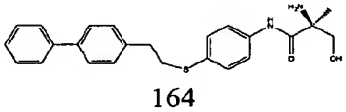

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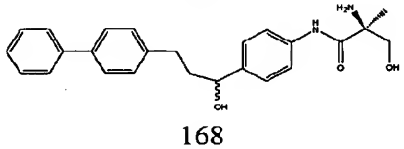

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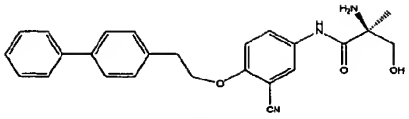

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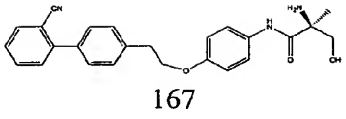

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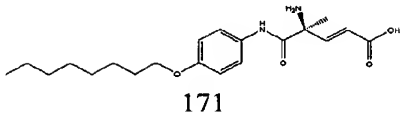

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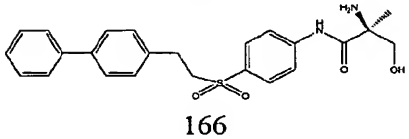

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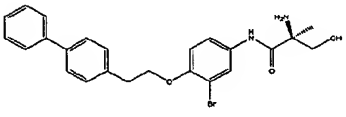

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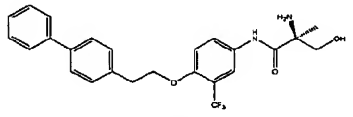

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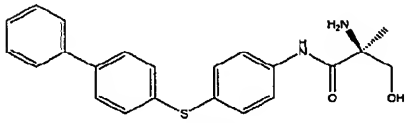

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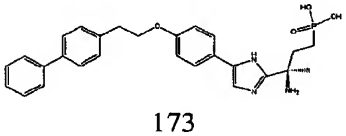

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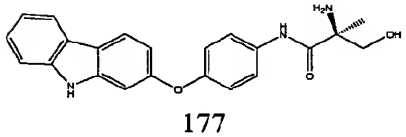

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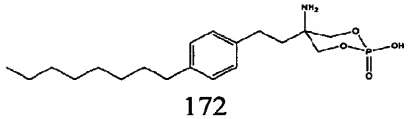

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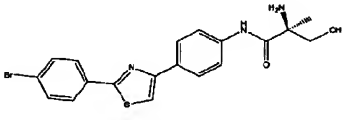

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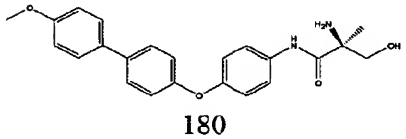

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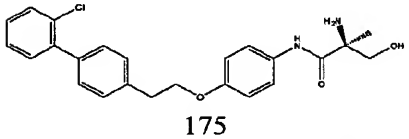

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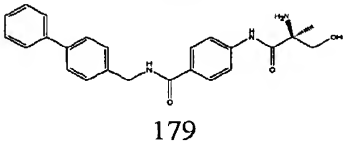

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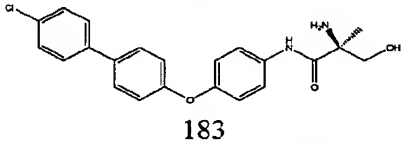

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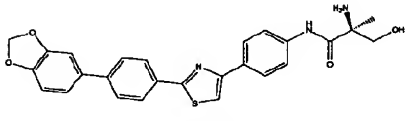

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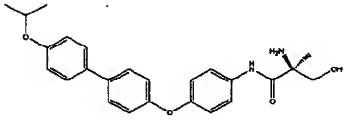

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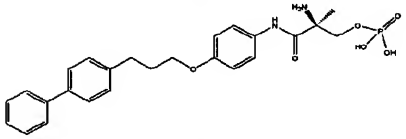

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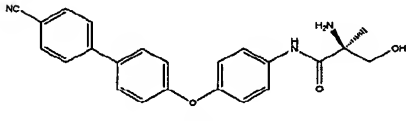

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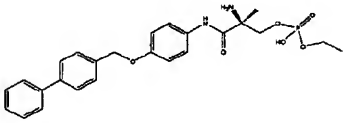

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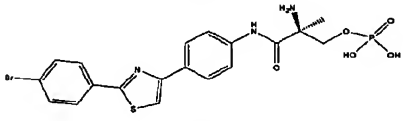

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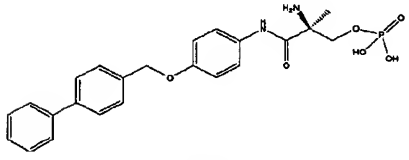

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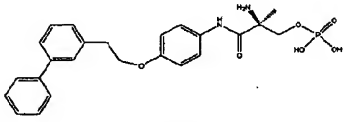

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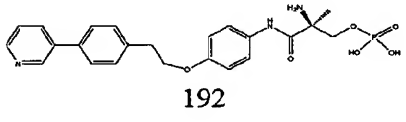

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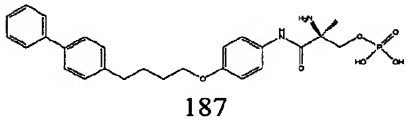

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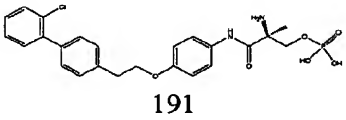

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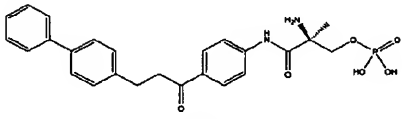

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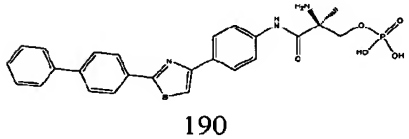

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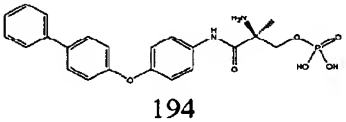

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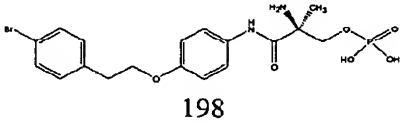

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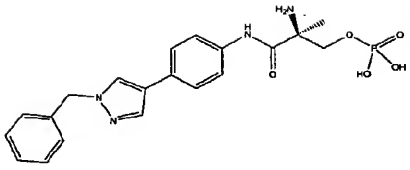

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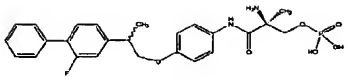

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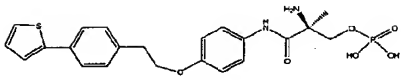

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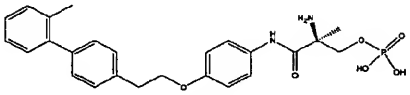

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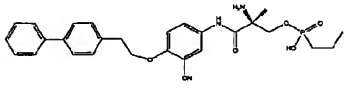

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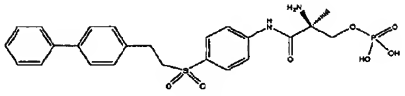

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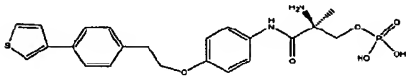

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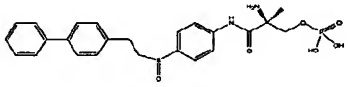

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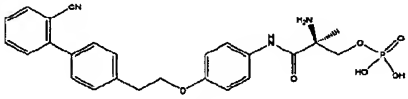

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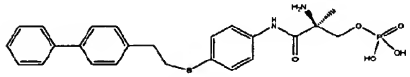

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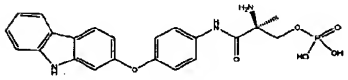

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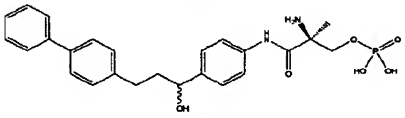

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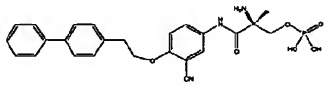

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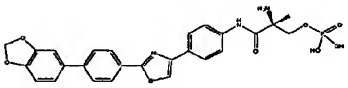

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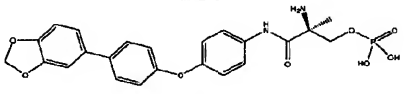

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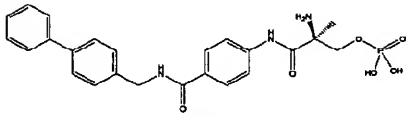

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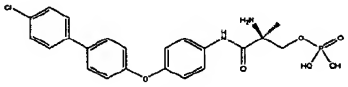

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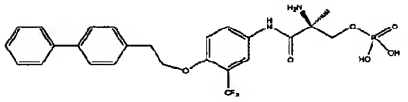

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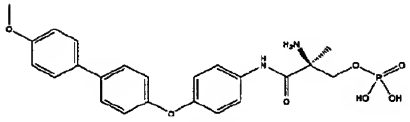

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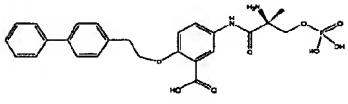

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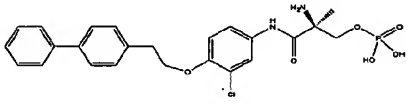

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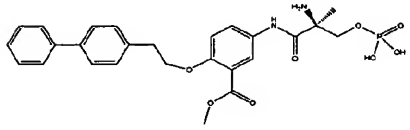

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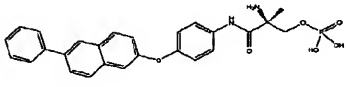

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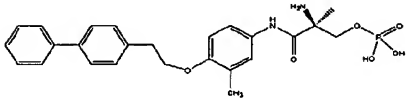

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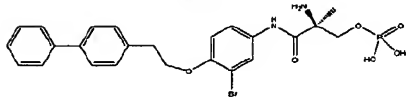

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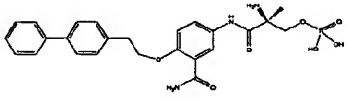

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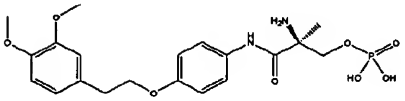

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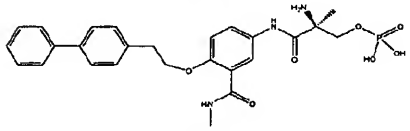

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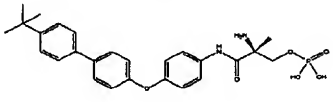

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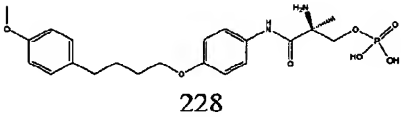

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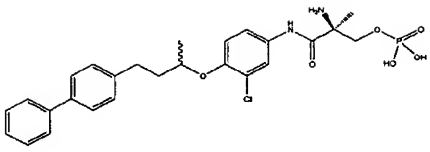

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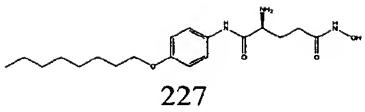

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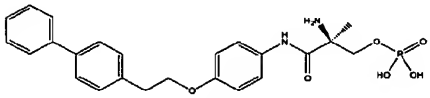

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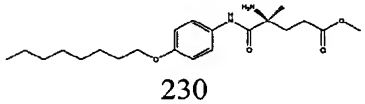

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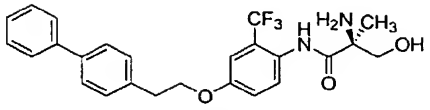

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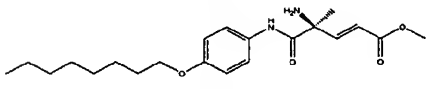

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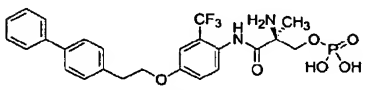

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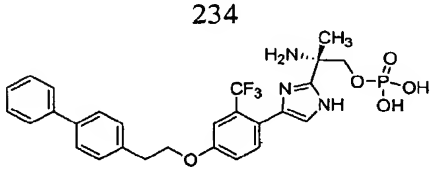

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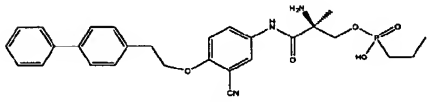

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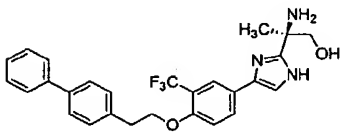

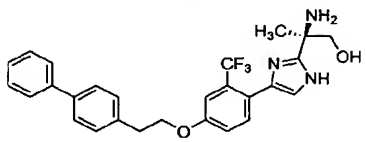

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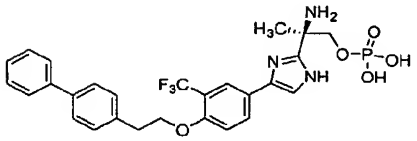
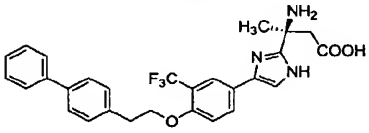
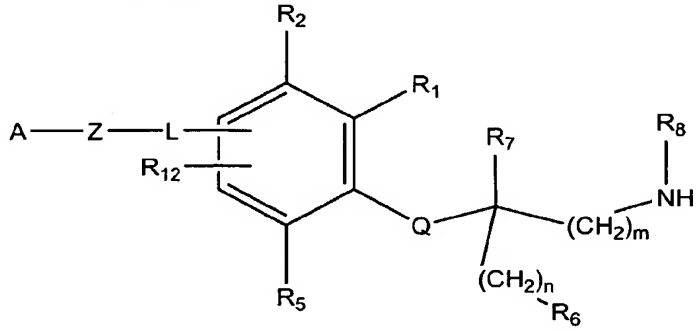


and



40. A method for treating a sphingosine 1-phosphate associated disorder in a subject, comprising administering to said subject an effective amount of a compound of formula (IV), such that said subject is treated for said sphingosine 1-phosphate associated disorder, wherein said compound of formula (IV) is:



(IV),

wherein:

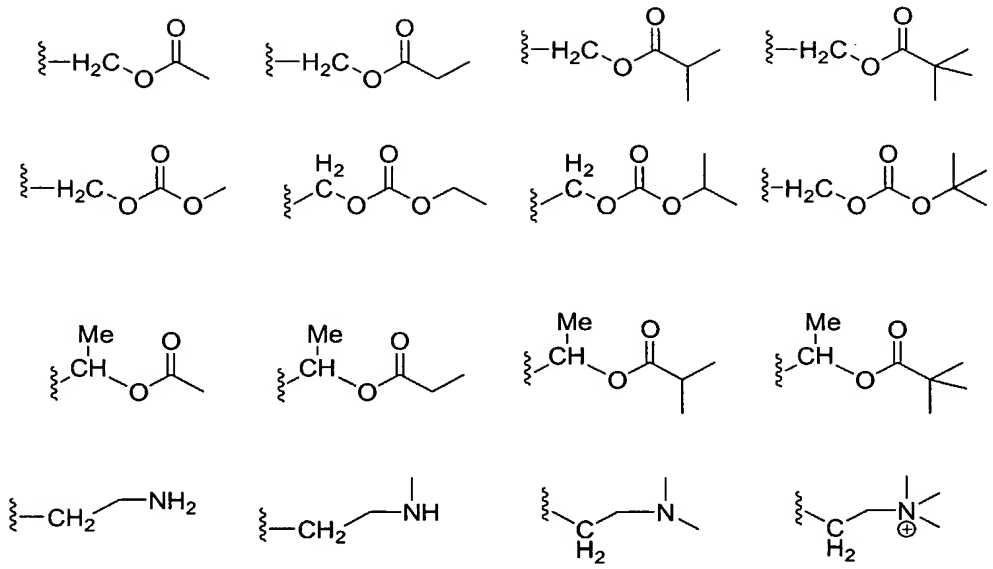
L is alkoxy, a covalent bond, substituted or unsubstituted alkyl, alkylcarbonyl, thioether, alkylsulfonyl, alkylcarbonylamino, alkylaminocarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, or substituted or unsubstituted heteroaryl;

Z and A are each independently substituted or unsubstituted aryl, wherein Z and A may be linked by a covalent bond, substituted or unsubstituted alkyl, NH, alkyloxy, O, thioether, S, aminocarbonyl, carbonylamino, carbonyloxy, or oxycarbonyl;

R^1, R^2, R^5 and R^{12} are each independently selected from the group consisting of hydrogen, halogen, cyano, substituted or unsubstituted aryl, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', wherein R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2;

Q is $-CH_2NR-$, $-CH_2NR(CO)-$, $-NH(CO)-$, $-(CO)NH-$, $-(CO)-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NRSO_2-$, $-SO_2-NR-$ or heteroaryl, where R is hydrogen or straight chain or branched C_1-C_6-alkyl;

R^6 is –OH, $-CO_2R^9$, $-CH_2=CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R10 and R11 are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



R^7 is H, C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, aryl, or together with R8 form a C_2-C_5-alkylene or a C_2-C_5-alkenylene group;

R^8 is H or C_1-C_6-alkyl; and

m and n are each, independently, an integer from 0 to 3;

provided that when R^4 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^3 and R^5 is not hydrogen; and when R^3 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^4 and R^5 is not hydrogen; and pharmaceutically acceptable salts thereof.

41. The method of claim 40, wherein said compound of formula (IV) is a compound of any one of claims 2-39.

42. The method of claim 40 or 41, wherein said subject is a human.

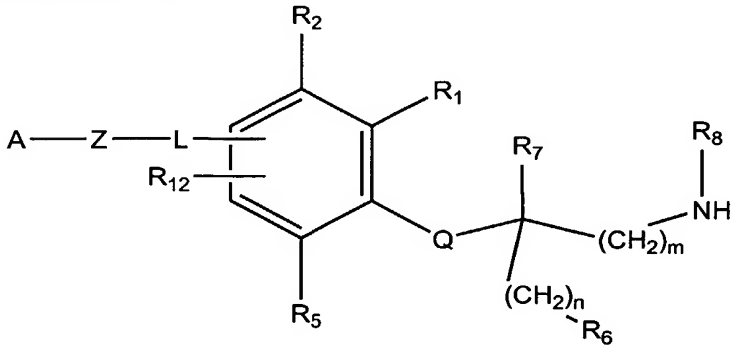
43. The method of any one of claims 40-42, wherein said sphingosine 1-phosphate associated disorder is associated with an inappropriate immune response.

44. The method of claim 40, wherein said subject is suffering from an autoimmune disorder or transplant rejection.

45. The method of claim 40, wherein said compound is an agonist of a sphingosine 1-phosphate 1 receptor.

46. The method of claim 45, wherein said compound is a selective agonist of the sphingosine 1-phosphate 1 receptor.

47. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (IV) and a pharmaceutically acceptable carrier, wherein said compound of formula (IV) is:



(IV)

wherein:

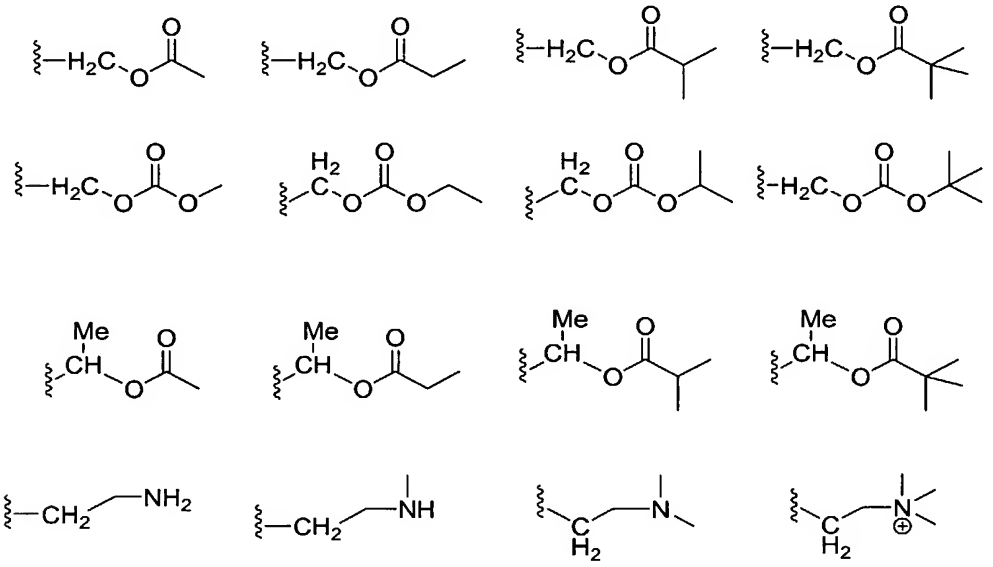
L is alkoxy, a covalent bond, substituted or unsubstituted alkyl, alkylcarbonyl, thioether, alkylsulfonyl, alkylcarbonylamino, alkylaminocarbonyl, alkyloxycarbonyl, alkylcarbonyloxy, or substituted or unsubstituted heteroaryl;

Z and A are each independently substituted or unsubstituted aryl, wherein Z and A may be linked by a covalent bond, substituted or unsubstituted alkyl, NH, alkyloxy, O, thioether, S, aminocarbonyl, carbonylamino, carbonyloxy, or oxycarbonyl;

R^1, R^2, R^5 and R^{12} are each independently selected from the group consisting of hydrogen, halogen, cyano, substituted or unsubstituted aryl, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl, C_1-C_6-alkyl-SO_2 or N(R)R', wherein R and R' are each independently hydrogen, straight chain or branched C_1-C_6-alkyl, straight chain or branched C_1-C_6-alkoxy, straight chain or branched halo-C_1-C_6-alkyl, straight chain or branched halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, hydroxyl-C_1-C_6-alkyl, carboxy-C_1-C_6-alkyl or C_1-C_6-alkyl-SO_2;

Q is $-CH_2NR-$, $-CH_2NR(CO)-$, $-NH(CO)-$, $-(CO)NH-$, $-(CO)-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$, $-NRSO_2-$, $-SO_2-NR-$ or heteroaryl, where R is hydrogen or straight chain or branched C_1-C_6-alkyl;

R^6 is –OH, $-CO_2R^9$, $-CH_2=CH(CO)OR^9$, $-OPO_2R^{10}R^{11}$, $-OPO_3R^{10}R^{11}$, $-CH_2PO_3R^{10}R^{11}$, $-OPO_2(S)R^{10}R^{11}$ or $-C(Y)(X)PO_3R^{10}R^{11}$, where X is hydroxyl or halide and Y is H or halide; or analogues of other carboxylate, phosphate or phosphonate isosteres not limited to those shown below; R^9 is H, straight chain or branched C_1-C_6-alkyl, or a substituted or unsubstituted aryl group; R10 and R11 are each independently H, straight chain or branched C_1-C_6-alkyl, a substituted or unsubstituted aryl group or selected from, but not limited to, the prodrugs listed below:



R^7 is H, C_1-C_6-alkyl, hydroxy-C_1-C_6-alkyl, aryl, or together with R8 form a C_2-C_5-alkylene or a C_2-C_5-alkenylene group;

R^8 is H or C_1-C_6-alkyl; and

m and n are each, independently, an integer from 0 to 3;

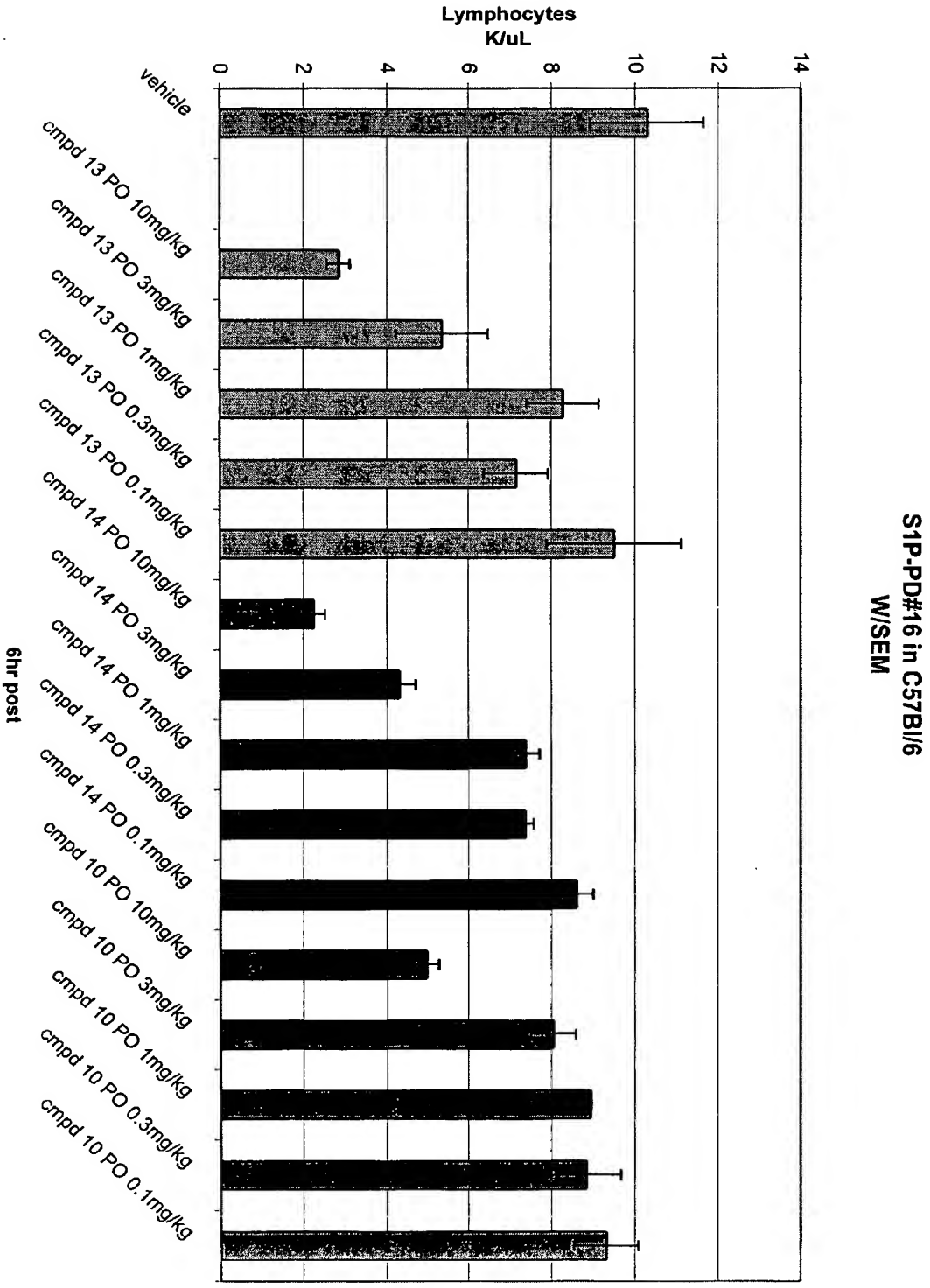
provided that when R^4 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^3 and R^5 is not hydrogen; and when R^3 is C_4-C_{20}-alkyl, at least one of R^1, R^2, R^4 and R^5 is not hydrogen; and pharmaceutically acceptable salts thereof.

48. The pharmaceutical composition of claim 47, wherein said pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

49. The pharmaceutical composition of claim 47, wherein said therapeutically effective amount is effective to treat a sphingosine 1-phosphate associated disorder.

50. The pharmaceutical composition of claim 49, wherein said sphingosine 1-phosphate associated disorder is associated with an inappropriate immune response.

51. The pharmaceutical composition of any one of claims 47-50, wherein said compound of formula (IV) is a compound of any one of claims 2-39.


Lymphocytes
K/uL
0
2
4
6
8
10
12
14
vehicle
cmpd 13 PO 10mg/kg
cmpd 13 PO 3mg/kg
cmpd 13 PO 1mg/kg
cmpd 13 PO 0.3mg/kg
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cmpd 14 PO 3mg/kg
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cmpd 14 PO 0.1mg/kg
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cmpd 10 PO 0.3mg/kg
cmpd 10 PO 0.1mg/kg
6hr post
S1P-PD#16 in C57Bl/6
W/SEM

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/028914

A. CLASSIFICATION OF SUBJECT MATTER

C07C237/04 C07F9/09 C07D233/54 C07D333/16 C07D317/64
C07D277/28 C07C323/41 C07C237/42 C07D261/08 C07D307/42
C07D213/30 A61K31/165 A61K31/415 A61K31/66 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C C07F C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/024673 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; BUEHLMAYER, PETER; HINTERDING, KLAU) 25 March 2004 (2004-03-25) cited in the application examples 23,27,28,31,32,49,50,71 page 29, table, compounds 49,50 claim 10	1-51
Y	WO 03/061567 A (MERCK & CO., INC; DOHERTY, GEORGE, A; FORREST, MICHAEL, J; HAJDU, RICH) 31 July 2003 (2003-07-31) cited in the application page 3, line 25 - line 32 examples	1-51

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 November 2005	28/11/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fitz, W

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/028914

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/064616 A (UNIVERSITY OF VIRGINA PATENT FOUNDATION; MACDONALD, TIMOTHY, L; LYNCH,) 22 August 2002 (2002-08-22) cited in the application page 14, line 5 - line 21 page 50 - page 51; example 3 claims 1-3	1-51
Y	WO 2004/010949 A (UNIVERSITY OF VIRGINIA PATENT FOUNDATION; LYNCH, KEVIN, R; MACDONALD,) 5 February 2004 (2004-02-05) cited in the application page 89, line 4 figures 6a,6b	1-51
P,A	WO 2005/041899 A (UNIVERSITY OF VIRGINIA PATENT FOUNDATION; LYNCH, KEVIN, R; MACDONALD,) 12 May 2005 (2005-05-12) cited in the application abstract	1,39,40, 47

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

[redacted]national application No.
PCT/US2005/028914

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 40-46 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/028914

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004024673 A	25-03-2004	AU 2003273865 A1	30-04-2004
		BR 0314113 A	12-07-2005
		CA 2497067 A1	25-03-2004
		CN 1681770 A	12-10-2005
		EP 1539674 A1	15-06-2005
WO 03061567 A	31-07-2003	CA 2472680 A1	31-07-2003
		EP 1469863 A2	27-10-2004
WO 02064616 A	22-08-2002	CA 2437358 A1	22-08-2002
		EP 1383778 A2	28-01-2004
		JP 2004529100 T	24-09-2004
WO 2004010949 A	05-02-2004	AU 2003259296 A1	16-02-2004
		EP 1546110 A2	29-06-2005
WO 2005041899 A	12-05-2005	NONE	